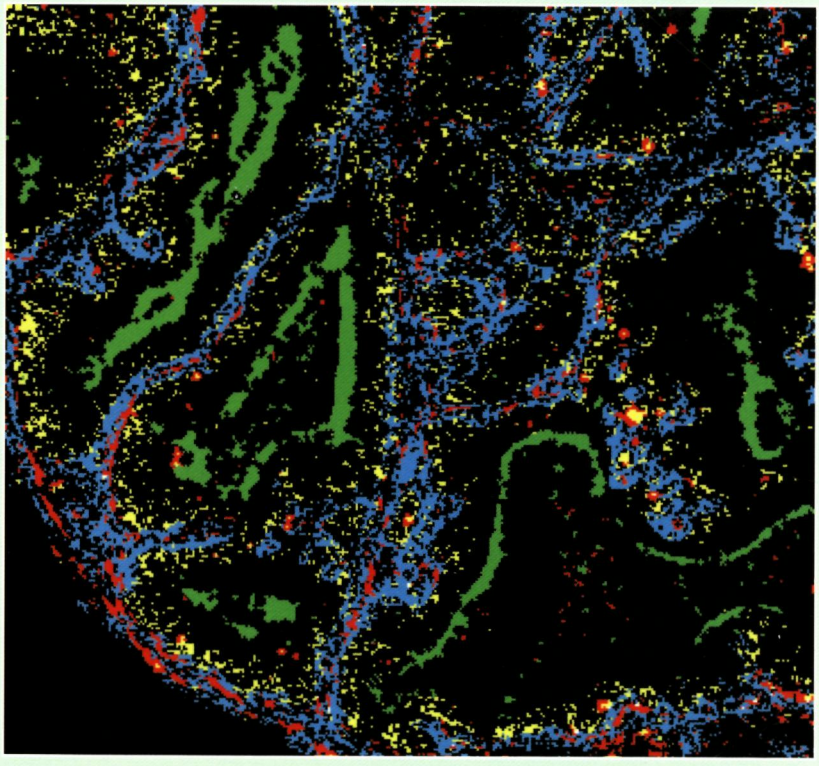
ACCELERATED RADIOTHERAPY WITH CARBOGEN AND NICOTINAMIDE FOR CARCINOMAS OF THE HEAD AND NECK

A study on feasibility, toxicity and tumor response



Hans Kaanders

ACCELERATED RADIOTHERAPY WITH CARBOGEN AND NICOTINAMIDE FOR CARCINOMAS OF THE HEAD AND NECK

A STUDY ON FEASIBILITY, TOXICITY AND TUMOR RESPONSE

Cover: Computerized microscopic image of a human larynx carcinoma showing vascular structures (red), blood perfusion (blue), proliferating cells (yellow) and hypoxic regions (green).

ISBN 90-901228-1

ACCELERATED RADIOTHERAPY WITH CARBOGEN AND NICOTINAMIDE FOR CARCINOMAS OF THE HEAD AND NECK

A STUDY ON FEASIBILITY, TOXICITY AND TUMOR RESPONSE

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Katholieke Universiteit Nijmegen,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op
woensdag 9 december 1998
des namiddags om 1.30 uur precies

door

Johannes Hendrikus Antonius Maria Kaanders
geboren op 10 mei 1959 te Vught

Promotores:	Prof. dr. A.J. van der Kogel
	Prof. dr. W.A.J. van Daal
Manuscriptcommissie:	Prof. dr. P. van den Broek
	Prof. dr. J.W.H. Leer
	Prof. dr. P H.M. de Mulder

Publication of this thesis was financially supported by:
Glaxo-Wellcome B.V , Janssen-Cilag B.V. and Schering-Plough B.V.

CONTENTS

CHAPTER 1

INTRODUCTION AND OUTLINE OF THE THESIS

Introduction

Radiotherapy is a cornerstone of cancer treatment, both for cure and for palliation In the curative setting radiotherapy is attractive because of its potential for organ preservation This is particularly evident with the treatment of head and neck cancer, the typical example being early laryngeal carcinomas where cure rates of 66-93% can be obtained with radiotherapy alone while preserving natural speech [1] Control rates drop however for the more advanced stages and still often for these patients surgery is preferred Already for many decades the challenge for radiation oncologists has been to increase the effectiveness of their treatment to apply it successfully also for more advanced local disease Efforts have typically been focussed on three major radiation resistance mechanisms intrinsic radioresistance, hypoxia, and tumor cell repopulation

Factors determining radiation response - intrinsic radiosensitivity

Among the first observations by the early pioneers of radiotherapy was that the radiosensitivity of tumors varies with histologic type A categorization into three groups was proposed by Paterson [38] He classified embryonic tumors and reticuloses (malignant lymphomas nowadays) as "radiosensitive", squamous cell carcinomas and adenocarcinomas as of intermediate radiosensitivity", and sarcomas and melanomas as "radioresistant" Work in the early eighties showed that there is a correlation between the radiosensitivity of human tumor cell lines measured by clonogenic cell survival assay and the clinical responsiveness of the tumors from which the cells were derived [9, 13] The logical approach to improve the cure rate of radioresistant tumors is to increase the dose This requires sparing of normal tissues to limit side-effects Methods aimed to reduce the volume of normal tissue irradiated include brachytherapy and, more recently, conformal radiotherapy Shortly after the discovery of radium by Marie Curie and Becquerel in 1898, brachytherapy was already applied to the treatment of malignant tumors and is now routinely used for various tumor sites Computed tomography (CT) and advanced computers allowing three-dimensional radiation treatment planning facilitate the delivery of external beam radiotherapy to selected (conformed) target volumes while sparing adjacent normal tissues Currently dose-escalation studies with conformal radiotherapy are ongoing for prostate and bronchus carcinoma [18, 39]

Another, biology based, method is hyperfractionation which is the application of a larger number of smaller dose fractions to deliver a higher total dose relative to conventional fractionation The rationale for this method is that late responding normal tissues have a greater fractionation sensitivity than acutely responding tissues including tumors The goal

is to improve the tumor control rate without increasing the incidence or severity of late sequelae. Randomized clinical trials indicate improved tumor control rates in head and neck cancer and bladder cancer [12, 23]. There is however some debate as to whether there is indeed an improvement of the therapeutic ratio because some studies also report a corresponding increase of late sequelae [3, 44].

Factors determining radiation response - tumor proliferation kinetics

During the last two decades, cellular repopulation has been recognized as an important cause for radiation treatment failure in various cancers, particularly squamous cell carcinomas [26, 28, 33, 45, 50]. Analysis of response of human tumors to fractionation schedules with varying overall times has shown that one week of prolongation can result in a 3-25% loss of local control [15]. Trott et al. attributed this to a shut down of the differentiation pathway and recruitment of cells into the proliferating compartment as a response to the radiation injury in the tumor tissue [47]. An alternative, or possibly coexistent, mechanism might be a reduction in the extent of natural cell loss, rather than an altered rate of cell production [14]. Fowler hypothesized that natural cell loss decreases during fractionated irradiation because of improved oxygen and nutritional supply as a consequence of shrinkage of the tumor cords surrounding blood vessels. Thus the effective tumor volume doubling time can shorten from values of around 3 months before therapy to potential doubling times of 3-6 days during a treatment course. Irrespective of the exact underlying mechanisms, there can be no doubt that with more time allowed for clonogenic repopulation, the chances of definitive tumor control will decrease. The importance of treatment duration is strongly supported by studies in experimental tumors [10, 25, 42].

A method to shorten the overall treatment time is by delivering multiple fractions per day during the whole or a part of the treatment. This is called accelerated radiotherapy. There is now evidence from randomized clinical studies that patients with head and neck and bronchus carcinomas benefit from this strategy to counteract repopulation of tumor clonogens [2, 11, 22, 36, 43]. However, it is also becoming clear from these studies that certain categories of patients profit more from this approach than others. There is now a need to find tumor characteristics that allow identification of these patients.

Factors determining radiation response - tumor oxygenation

Oxygen strongly influences the biological effects of ionizing radiation. The importance of the "oxygen effect" to radiotherapy was recognized by Mottram [29] and later worked out in greater detail for mammalian tissues by Gray et al. [17]. Typically, hypoxic cells are three times more radioresistant than well oxygenated cells, at least at doses of 3 Gy and higher.

There is evidence that at lower (but clinically relevant) doses this enhancement of radiation damage by oxygen is somewhat less and in the order of a factor of 2 5 [37] Thomlinson and Gray described the classical "diffusion-limited" hypoxia model with hypoxic tumor cells located at a relatively constant distance from blood vessels, the diffusion distance of oxygen in tissue [46] This is now also called "chronic" hypoxia Later it was postulated that tumor hypoxia could also result from local and temporary fluctuations in tumor blood perfusion, so called "acute" or "transient" hypoxia [4]

Hypoxia appears to be present in the majority of rodent solid tumors and in xenografted human tumors [30, 40, 48] Estimates of hypoxic fractions range from below 1% to as high as 95% and depend on the methods used for measuring hypoxia, tumor size, transplantation site, and characteristics of the host There is also substantial evidence for hypoxia in human tumors in situ [7] However, the oxygenation status cannot be reliably predicted from histology or tumor volume and thus needs to be measured in individual cases There are indications that tumor oxygenation predicts the prognosis of patients receiving radiotherapy for carcinomas of the uterine cervix and the head and neck and for soft tissue sarcomas [16, 21, 31, 32]

A number of strategies to overcome hypoxic cell radioresistance have been tested in the clinic These include the use of normobaric or hyperbaric high oxygen-content gasses, vasoactive agents that increase blood flow, blood transfusions or artificial oxygen-carrying blood substances (perfluorocarbons), stimulation of hemoglobin production by erythropoietin, and hypoxic cell radiosensitizers Other methods such as hyperthermia and bioreductive drugs preferentially kill hypoxic cells and can be used in combination with radiotherapy A meta-analysis of 72 randomized clinical trials of radiotherapy either alone or combined with a treatment to modify tumor hypoxia showed improvement of loco-regional control and survival following manipulation of tumor hypoxia [34] When analyzed according to site, this improvement was dominated by the head and neck tumors Three randomized studies, two in head and neck carcinoma and one in carcinoma of the uterine cervix, demonstrated improved loco-regional control and survival after radiotherapy in hyperbaric oxygen relative to treatment in air [19, 20, 49] A recent randomized study showed increased tumor control and survival advantage in patients with supraglottic and pharynx carcinomas with the hypoxic radiosensitizer nimorazole [35] However, as with altered fractionation regimens, there are indications from these clinical trials that certain subgroups of patients will benefit from hypoxia modification more than others

Outline of the thesis

For each of the above discussed radioresistance mechanisms there are examples of clinical studies proving that counteracting these mechanisms can be beneficial for treatment outcome The gain, expressed in terms of loco-regional tumor control, is in the range of 5 to 23% [2, 8, 11, 19, 20, 22, 23, 35, 36, 43, 49] These are important improvements but, also with these new approaches, still a significant proportion of the cases remains uncontrolled Often in the analyses certain subgroups of patients emerged that did particularly well on the investigational treatment Furthermore, although one of the resistance mechanisms may dominate in a certain tumor, there is no reason to assume that the other mechanisms will not influence treatment outcome

Future work should therefore concentrate on the following objectives

1) Identification of tumors or classes of tumors that are most effectively treated by either of the new radiotherapy approaches
2) Combination of treatment modifications that counteract different radioresistance mechanisms

The aim of this work was to prepare a strategy which combines methods for hypoxic modification with accelerated radiotherapy for application in the clinic The feasibility and toxicity of this treatment were investigated in head and neck cancer patients Subsequently its effectiveness in patients with advanced laryngeal cancer was assessed

A schedule for accelerated fractionated radiotherapy was designed employing moderate reduction of overall treatment time with unchanged total dose and dose per fraction relative to conventional treatment This was accomplished by delivering two fractions per day during the last part of the treatment A secondary but not unimportant advantage of this schedule is that it does not increase workload on the treatment machines because the number of fractions remains unchanged In **chapter 2** the toxicity of this schedule was compared to that of conventional treatment in patients with laryngeal cancer

After this study it was concluded that the schedule is feasible but that further shortening of overall treatment time without reduction of total dose may lead to unacceptable acute and, possibly, also late mucosal toxicity **Chapter 3** reviews the experimental and clinical data on radiation mucositis available in the literature in order to assess whether indeed the upper aerodigestive tract mucosa is limiting to treatment intensification by altered fractionation The clinical data indicate that, relative to a conventional treatment of 7 weeks, the maximum achievable gain in treatment time is 2 weeks with the mucosa being the limiting tissue Any

further acceleration requires a reduction of dose which can be disadvantageous, in particular for tumors with lower intrinsic radiosensitivity

One strategy to further improve the treatment outcome can be to combine accelerated radiotherapy with hypoxic modifiers Studies in rodent tumors demonstrated significant sensitization when **A**ccelerated fractionated **R**adiotherapy was administered together with a combination of **C**arb**O**gen and **N**icotinamide ("**ARCON**") [41, 42] Carbogen is a gas mixture containing 95% oxygen and 5% carbon dioxide and breathing of this mixture causes a rise of the oxygen partial pressure in the blood and tissues With the use of an immunohistochemically detectable hypoxic marker it was demonstrated that carbogen very effectively reduced diffusion-limited hypoxia in xenografted human laryngeal carcinomas [5] This effect of carbogen was also shown in patients with head and neck tumors by direct measurements with oxygen electrodes in metastatic lymph nodes [27] Nicotinamide, the amide derivative of vitamin B_3, can reduce the intermittent closure of blood vessels in experimental rodent tumors and consequently decrease transient hypoxia [6, 24] With carbogen an enhancement ratio of 1 5 was obtained in mouse tumors with radiation doses close to those used clinically This means that, to obtain the same tumor control rate as with radiotherapy alone, a 1 5 times lower radiation dose was needed when radiotherapy was given in combination with carbogen Addition of nicotinamide gave further radiosensitization to an enhancement ratio of 1 7 Finally, when also accelerated fractionation was incorporated, the complete ARCON treatment resulted in an enhancement ratio of 1 9 indicating an almost twofold increase of the effectiveness of this treatment relative to conventional radiotherapy alone [42] These promising results justified testing of this treatment in the clinic

For this purpose patients with squamous cell carcinomas of the head and neck were selected because there was already evidence that this category can benefit both from acceleration and from hypoxic modification Additional arguments were that the loco-regional control rate for the more advanced cases is not yet satisfactory and that organ preservation in the head and neck region is of great value Finally, this region is easily accessible for assessment of normal tissue reactions and tumor response and thus is attractive as a "test site" for new treatments

For administration of carbogen a dependable and convenient breathing system was required which could be combined with techniques for immobilization of the patient A method based on professional diving equipment was developed and is presented in **chapter 4**

After experience was gained with a schedule for accelerated fractionation (chapter 2), carbogen and nicotinamide were added to this treatment in consecutive steps **Chapter 5**

reports on the feasibility and toxicity of these components. It was concluded that radiotherapy combined with carbogen and nicotinamide is a safe treatment with manageable side-effects. Based on experience with nicotinamide in other diseases it was suggested that this is a relatively non-toxic agent with a low incidence of side-effects even at the high dose levels required to obtain the sensitizing effect. However, gastrointestinal side-effects were observed frequently in the head and neck patients and severe renal toxicity was observed in a few. Recommendations to improve the safe use of nicotinamide were formulated and the pharmacokinetics, tolerance, and compliance to the drug were further investigated which is described in **chapter 6**.

Chapter 7 presents the outcome of the new treatment in 62 patients with stage III-IV squamous cell carcinoma of the larynx. The literature on radiotherapy for advanced laryngeal cancer is briefly reviewed and results are compared with the outcome of the current study.

Chapter 8 provides a summary of this work.

References

1. Ang, K.K., Kaanders, J.H.A.M. and Peters, L.J. Radiotherapy for head and neck cancers: indications and techniques. pp 82-85. Lea & Febiger, Philadelphia, PA, 1994.

2. Ang, K.K., Trotti, A., Garden, A.S. et al. Overall time factor in postoperative radiation: results of a prospective randomized trial. Radiother. Oncol. 40 (Suppl 1): S30, 1996.

3. Beck-Bornholdt, H.-P., Dubben, H.-H., Liertz-Petersen, C. and Willers, H. Hyperfractionation: where do we stand? Radiother. Oncol. 43: 1-21, 1997.

4. Brown, J.M. Evidence for acute hypoxic cells in mouse tumours and a possible mechanism of reoxygenation. Br. J. Radiol. 52: 650-656, 1979.

5. Bussink, J., Kaanders, J.H.A.M., Rijken, P.F.J.W. et al. Vascular architecture and microenvironmental parameters in human squamous cell carcinoma xenografts: effects of carbogen and nicotinamide. Radiother. Oncol., accepted.

6. Chaplin, D.J., Horsman, M.R. and Trotter, M.J. The effect of nicotinamide on the microregional heterogeneity of oxygen delivery within a murine tumour. J. Natl. Cancer Inst. 82: 672-676, 1990.

7. Chapman, J.D. Measurement of tumor hypoxia by invasive and non-invasive procedures: a review of recent clinical studies. Radiother. Oncol. 20 (Suppl.): 13-19, 1991.

8. Cummings, B.J., Keane, T.J., O'Sullivan, B. et al. A prospective randomized trial of hyperfractionated versus conventional once daily radiation for advanced squamous cell carcinomas of the larynx and pharynx. Radiother. Oncol. 40 (Suppl 1): S30, 1996.

9. Deacon, J., Peckham, M.J. and Steel, G.G. The radioresponsiveness of human tumours and the initial slope of the cell survival curve. Radiother. Oncol. 2: 317-323, 1984.

10. Denekamp, J. Cell kinetics and radiation biology. Int. J. Radiat. Biol. 49: 357-380, 1986.

11. Dische, S., Saunders, M.I., Barrett, A., Harvey, A., Gibson, D. and Parmar, M.K.B. A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother. Oncol. 44: 123-136, 1997.

12. Edsmyr, F., Andersson, L., Esposti, P.L., Littbrand, B. and Nilsson, B. Irradiation therapy with multiple small fractions per day in urinary bladder cancer. Radiother. Oncol. 4: 197-203, 1985.

13. Fertil, B. and Malaise, E.P. Intrinsic radiosensitivity of human cell lines is correlated with radioresponsiveness of human tumors: analysis of 101 published survival curves. Int. J. Radiat. Oncol. Biol. Phys. 11: 1699-1707, 1985.

14. Fowler, J.F. The phantom of tumor treatment - continually rapid proliferation unmasked. Radiother. Oncol. 22: 156-158, 1991.

15. Fowler, J.F. and Lindstrom, M.J. Loss of local control with prolongation in radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 23: 457-467, 1992.

16. Gatenby, R.A., Kessler, H.B., Rosenblum, J.S. et al. Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 14: 831-838, 1988.

17. Gray, L.H., Conger, A.D., Ebert, M., Hornsey, S., and Scott, O.C.A. The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br. J. Radiol. 26: 638-648, 1953.

18. Hanks, G.E., Schultheiss, T.E., Hanlon, A.L. et al. Optimization of conformal radiation treatment of prostate cancer: a report of a dose escalation study. Int. J. Radiat. Oncol. Biol. Phys. 37: 543-550, 1997.

19. Henk, J.M. Late results of a trial of hyperbaric oxygen and radiotherapy in head and neck cancer: a rationale for hypoxic cell sensitizers? Int. J. Radiat. Oncol. Biol. Phys. 12: 1339-1341, 1986.

20. Henk, J.M., Kunkler, P.B. and Smith, C.W. Radiotherapy and hyperbaric oxygen in head and neck cancer. Lancet ii: 101-103, 1977.

21. Höckel, M., Schlenger, K., Mitze, M., Schäffer, U. and Vaupel, P. Hypoxia and radiation response in human tumors. Sem. Radiat. Oncol. 6: 3-9, 1996.

22. Horiot, J.C., Bontemps, P., van den Bogaert, W. et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother. Oncol. 44: 111-121, 1997.

23. Horiot, J.C., Le Fur, R., N'Guyen, T. et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother. Oncol. 25: 231-241, 1992.

24. Horsman, M.R., Chaplin, D.J. and Overgaard, J. Combination of nicotinamide and hyperthermia to eliminate radioresistant chronically and acutely hypoxic tumour cells. Cancer Res. 50: 7430-7436, 1990.

25. Kummermehr, J., Dörr, W. and Trott, K.R. Kinetics of accelerated repopulation in normal and malignant squamous epithelia during fractionated radiotherapy. Br. J. Radiol. 24 (Suppl.): 193-199, 1992.

26. Maciejewski, B., Withers, H.R., Taylor, J.M.G. and Hliniak, A. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx: tumor dose-response and repopulation. Int. J. Radiat. Oncol. Biol. Phys. 16: 831-843, 1989.

27. Martin, L., Lartigau, E., Weeger, P. et al. Changes in the oxygenation of head and neck tumors during carbogen breathing. Radiother. Oncol. 27: 123-130, 1993.

28. Maruyama, Y., Wierzbicki, J., Feola, J. and Urano, M. Regeneration in cervix cancer after ^{252}Cf neutron brachytherapy. Int. J. Radiat. Oncol. Biol. Phys. 19: 61-67, 1990.

29. Mottram, J.C. A factor of importance in the radiosensitivity of tumours. Br. J. Radiol. 9: 606-614, 1936.

30. Moulder, J.E. and Rockwell, S. Hypoxic fractions of solid tumors: experimental techniques, methods of analysis, and a survey of existing data. Int. J. Radiat. Oncol. Biol. Phys. 10: 695-712, 1984.

31. Nordsmark, M., Keller, J., Høyer, M., Nielsen, O.S. and Overgaard, J. Hypoxia in human soft tissue sarcomas is associated with poor survival. Radiother. Oncol. 48 (Suppl. 1): S162, 1998.

32. Nordsmark, M., Overgaard, M. and Overgaard, J. Pretreatment oxygenation predicts radiation response in advanced squamous cell carcinoma of the head and neck. Radiother. Oncol. 41: 31-39, 1996.

33. Overgaard, J., Hjelm-Hansen, M., Vendelbo Johansen, L. and Andersen, A.P. Comparison of conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx. Acta Oncol. 27: 147-152, 1988.

34 Overgaard, J and Horsman, M R Modification of hypoxia-induced radioresistance in tumors by the use of oxygen and sensitizers Sem Radiat Oncol 6 10-21, 1996

35 Overgaard, J , Sand Hansen, H , Overgaard, M et al A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma Results of the Danish Head and Neck Cancer Study (DAHANCA) protocol 5-85 Radiother Oncol 46 135-146, 1998

36 Overgaard, J , Sand Hansen, H , Overgaard, M et al Conventional radiotherapy as primary treatment of squamous cell carcinoma of the head and neck A randomized multicenter study of 5 versus 6 fractions per week - report from the DAHANCA 7 trial Int J Radiat Oncol Biol Phys 39 (Suppl) 188, 1997

37 Palcic, B and Skarsgard, L D Reduced oxygen enhancement ratio at low doses of ionizing radiation Radiat Res 100 328-339, 1984

38 Paterson, R P The radical x-ray treatment of the carcinomata Br J Radiol 9 671-679, 1936

39 Robertson, J M , Ten Haken, R K , Hazuka, M B et al Dose escalation for non-small cell lung cancer using conformal radiation therapy Int J Radiat Oncol Biol Phys 37 1079-1085, 1997

40 Rockwell, S and Moulder, J E Hypoxic fractions of human tumors xenografted into mice a review Int J Radiat Oncol Biol Phys 19 197-202, 1990

41 Rojas, A Radiosensitization with normobaric oxygen and carbogen Radiother Oncol 20 (Suppl 1) 65-70, 1991

42 Rojas, A , Hirst, V K , Calvert, A S and Johns, H Carbogen and nicotinamide as radiosensitizers in a murine mammary carcinoma using conventional and accelerated radiotherapy Int J Radiat Oncol Biol Phys 34 357-365, 1996

43 Saunders, M I , Dische, S , Barrett, A , Harvey, A , Gibson, D and Parmar, M K B Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer a randomised multicentre trial Lancet 350 161-165, 1997

44 Stuschke, M and Thames, H D Hyperfractionated radiotherapy of human tumors overview of the randomized clinical trials Int J Radiat Oncol Biol Phys 37 259-267, 1997

45. Taylor, J M G., Withers, H R and Mendenhall, W M Dose-time considerations of head and neck squamous cell carcinomas treated with irradiation Radiother. Oncol. 17 95-102, 1990.

46. Thomlinson, R H and Gray, L H The histological structure of some human lung cancers and the possible implications for radiotherapy Br. J. Cancer 9. 539-549, 1955.

47. Trott, K.R. and Kummermehr, J. Accelerated repopulation in tumours and normal tissues. Radiother Oncol 22. 159-160, 1991

48. Vaupel, P , Okunieff, P , Kallinowski, F and Neuringer, L J Correlations between ^{31}P-NMR spectroscopy and tissue O_2 tension measurement in a murine fibrosarcoma. Radiat Res. 120 477-493, 1989

49 Watson, E R., Halnan, K E , Dische, S et al. Hyperbaric oxygen and radiotherapy: a medical research council trial in carcinoma of the cervix Br J. Radiol 51 879-887, 1978

50. Withers, H R , Taylor, J M G and Maciejewski, B The hazard of accelerated tumor clonogen repopulation during radiotherapy Acta Oncol 27 131-146, 1988.

CHAPTER 2

ACCELERATED FRACTIONATION RADIOTHERAPY FOR LARYNGEAL CANCER, ACUTE AND LATE TOXICITY

Johannes H.A.M. Kaanders

Willem A.J. van Daal

Willem J. Hoogenraad

Albert J. van der Kogel

Reprinted from: Int. J. Radiat. Oncol. Biol. Phys. 24: 497-503, 1992

with permission from Elsevier Science

Abstract

The acute toxicity of an accelerated radiotherapy scheme was compared with a conventional schedule Eighteen patients with squamous cell carcinoma of the larynx were treated with accelerated fractionation radiotherapy An average reduction of the overall treatment time of 11 days was accomplished by giving two fractions a day during the last part of the treatment The total dose and fraction dose were left unchanged The acute reactions of skin and mucosa in these patients were compared with those in 40 patients treated with a conventional fractionation scheme, that is, 2 Gy per fraction, five fractions per week, to a total dose of 64-70 Gy

The acute reactions were maximal between 5 and 7 weeks after the start of treatment Complete healing occurred within 3 months in all patients The mucosal reactions and, as a consequence, dysphagia were clearly increased in those patients treated with accelerated fractionation For confluent mucositis an ED_{50} of 66 Gy was calculated compared to 69 Gy for conventional fractionation To a lesser degree, skin toxicity was also enhanced in the patients treated with the accelerated schedule

Severe edema of the laryngeal mucosa occurred only in patients treated to a total dose of 68 or 70 Gy and was somewhat more frequent with accelerated fractionation (4/10) than with conventional fractionation (4/24) One patient in the accelerated fractionation group underwent laryngectomy for persistent edema and laryngeal necrosis No severe late skin reactions were observed

It can be concluded that the fractionation schedule tested in this study is feasible Further shortening of the overall treatment time without reduction of the total dose will likely lead to unacceptable acute and, possibly, also late toxicity

Introduction

When treating laryngeal cancer by radiotherapy there is a need to optimize the irradiated volume, total dose, dose per fraction and overall treatment time Whether the conventional system of fractionation (i e 60-70 Gy in 2 Gy fractions, five times a week) is the optimal way of delivering radiotherapy in all circumstances is highly debatable at this moment [16, 19, 21]

Accelerated fractionation, as an alternative to conventional fractionation, is defined as shortening the overall treatment time without changing total dose nor fraction size, by giving two or three doses daily The rationale for attempting to improve the therapeutic ratio by accelerated fractionation is based primarily on the premise that shortening the overall treatment time reduces the opportunity for proliferation of tumor cells during treatment and, thereby, increases the probability of tumor control for a given dose level The acute normal tissue reactions will be exacerbated for the same reason, but assuming that repair is complete between fractions, one expects little or no change in the response of the slowly cycling target cells of late reacting tissues [4]

Withers et al analyzed the results of radiotherapy in head and neck cancer [22] Using the data of 59 clinical studies from the literature, they observed that after a lag period in the order of 4 weeks a dose increment of about 0 6 Gy for each additional day of treatment is needed for a constant level of tumor control They suggested that a net increased repopulation of tumor clonogens becomes effective after this lag period The same conclusions have been drawn from a retrospective clinical study [11] Several other clinical studies indicate that accelerated fractionation may be a promising treatment modality for head and neck cancer [1, 8, 15, 20]

These considerations prompted us to conduct a study on accelerated fractionation, concomitant boost type In contrast to other clinical studies where the total dose or dose per fraction were lowered to accomplish sufficient reduction of treatment time, we only shortened the overall treatment time without changes in other parameters We elected to study a well defined, homogeneous population, that is, patients with laryngeal cancer Our first goal was to evaluate and document the toxicity of the accelerated schedule in comparison with conventional daily fractionation which forms the basis of this report

Methods and materials

Only patients with histologically proven squamous cell carcinoma of the larynx were eligible for the study The tumors were staged according to the "TNM classification for malignant tumours" as defined by the UICC [7] Patients with T_1, T_2 or T_3 tumors, with or without neck node metastases but without distant metastases were included Informed consent was obtained after the nature of the procedure was explained All patients starting treatment between December 1st, 1987 and March 31st, 1988 were assigned to receive accelerated fractionation radiotherapy (AF) These patients were compared to consecutive patients treated by conventional fractionation radiotherapy (CF) between April 1st, 1988 and February 28th, 1989 The same criteria for tumor site, histology, and TNM-stage were used

All patients were treated on a linear accelerator using 4 MV photons The larynx and subdigastric and midjugular lymph nodes were irradiated through lateral parallel opposed portals except for T_1N_0 disease where only the larynx was included In patients presenting with nodal metastases an anterior appositional field was added to treat the lower neck nodes The boost dose to the primary tumor and involved lymph nodes was given through lateral photon fields

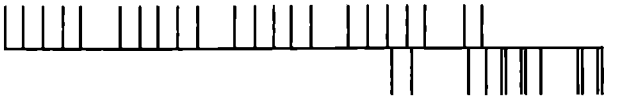
In our institution, conventional fractionation consists of a dose of 44 Gy, given to the initial target volume as described above This is followed by a boost to a total dose of 64-70 Gy, depending on T-stage (64 Gy for T_1 tumors, 68 Gy for T_2 and 70 Gy for T_3) The dose per fraction is 2 Gy and five fractions per week are given Overall treatment time is 44-50 days For those patients receiving accelerated fractionation radiotherapy, total dose and dose per fraction were the same as for those receiving conventional treatment The total treatment time, however, was reduced to 36-39 days This was achieved by giving two fractions a day in the last part of the treatment period (Fig 1), using a minimal interval of 6 h between fractions Dose specification was according to the recommendations of the ICRU in Report 29 [6] Computer planning was used for optimization of dose distribution

The patients were examined by two radiation oncologists at least once a week during and after treatment until the acute side-effects had subsided Skin and mucosal reactions as well as dysphagia were scored on a five-point scale (Table 1) The tumor response was assessed Subsequently the patients returned for follow-up every 2 months during the first year and every 3 months during the second year Late effects of irradiation were considered severe if there was ulceration of skin or mucous membranes, severe edema of the laryngeal mucosa or chondritis and/or necrosis of cartilage These items have been selected from the "system for recording of radiation-morbidity" as proposed by Lartigeau et al [10]

Table 1. *Scores for acute radiation reactions.*

	Acute reactions	Score
Skin	normal	0
	slight redness	1
	severe redness	2
	dry desquamation	3
	moist desquamation	4
Mucosa	normal	0
	slight redness	1
	severe redness	2
	spotted mucositis	3
	confluent mucositis	4
Dysphagia	normal	0
	complaints, no medication	1
	medication needed	2
	liquid feeding	3
	tube feeding	4

Conventional fractionation: total dose 70 Gy, dose per fraction 2 Gy, overall time 47 days (vertical bars below horizontal line indicate boost).



Accelerated fractionation: total dose 70 Gy, dose per fraction 2 Gy, overall time 37 days (vertical bars below horizontal line indicate boost)

Fig. 1. *Diagrammatic representation of the fractionation schemes used in the present study*

Mean values of the weekly toxicity scores were calculated for each treatment group Fisher's exact test was used to test the statistical significance of differences between treatment groups Spearman's correlation coefficient was calculated to test relationships between early and late effects

For calculation of isoeffective doses, dose-response curves were constructed by plotting the proportion of patients with a certain toxicity score versus radiation dose Where possible, ED_{50} values and confidence limits were calculated by probit analysis and compared by the chi-square test

Results

Eighteen patients were treated with accelerated fractionation Table 2 shows TNM-stage and total dose given The mean treatment time was 36 days for patients treated to 64 Gy and 38 days for patients treated to 68 or 70 Gy These 18 patients were compared to 40 controls who received conventional radiotherapy The mean treatment time for this latter group of patients was 47 days for those receiving 64 Gy and 49 days for those treated to 68 or 70 Gy The difference in overall treatment time between the AF-group and the CF-group was thus 11 days All patients completed the planned treatment without interruption Follow-up was 30-40 months for the CF-group and 39-42 months for the AF-group

Table 2. *Numbers of patients by stage, total dose, and fractionation schedule applied*

	CF-group		AF-group	
Stage	$T_{is}N_0M_0$	2	$T_1N_0M_0$	9
	$T_1N_0M_0$	14	$T_2N_0M_0$	7
	$T_2N_0M_0$	18	$T_2N_2M_0$	1
	$T_3N_0M_0$	6	$T_3N_0M_0$	1
Total dose	64 Gy	16	64 Gy	8
	68 Gy	18	68 Gy	9
	70 Gy	6	70 Gy	1
Total		40		18

Acute toxicity

Skin: The average skin reaction reached its peak between 5 and 7 weeks after the start of radiotherapy in both treatment groups (Fig. 2). Table 3 presents the proportion of patients that developed dry or moist desquamation. Moist desquamation was observed predominantly in those patients treated by accelerated fractionation and to a dose of 68-70 Gy. On the average this reaction level was reached on day 45 after the start of irradiation and persisted for 2 weeks. The skin reactions healed completely within 3 months after start of treatment in all patients.

Mucosa: The earliest mucosal reactions (redness) were observed 1 week after the start of treatment. As expected, reactions during the initial 4 weeks of treatment were comparable in both treatment groups since the first part of the irradiation schedule was identical for all patients. Maximal reactions usually consisted of spotted or confluent mucositis. The average score was highest 5 to 7 weeks after start of treatment (Fig. 3). The proportion of patients

Table 3. *Acute toxicity scores by fractionation schedule (CF = conventional fractionation, AF = accelerated fractionation) and total dose.*

	64 Gy		
	CF		**AF**
skin ≥ 3	3/16 (19%)	n.s.*	3/8 (38%)
skin = 4	0/16 (0%)	n.s.*	0/8 (0%)
mucosa ≥ 3	8/16 (50%)	$p = 0.02$*	8/8 (100%)
mucosa = 4	0/16 (0%)	n.s.*	1/8 (13%)
dysphagia ≥ 2	5/16 (31%)	n.s.*	5/8 (63%)
	68-70 Gy		
	CF		**AF**
skin ≥ 3	19/24 (79%)	n.s.*	9/10 (90%)
skin = 4	2/24 (8%)	$p = 0.01$*	5/10 (50%)
mucosa ≥ 3	17/24 (71%)	n.s.*	9/10 (90%)
mucosa = 4	11/24 (46%)	$p = 0.02$*	9/10 (90%)
dysphagia ≥ 2	12/24 (50%)	$p < 0.01$*	10/10 (100%)

*Fisher's exact test

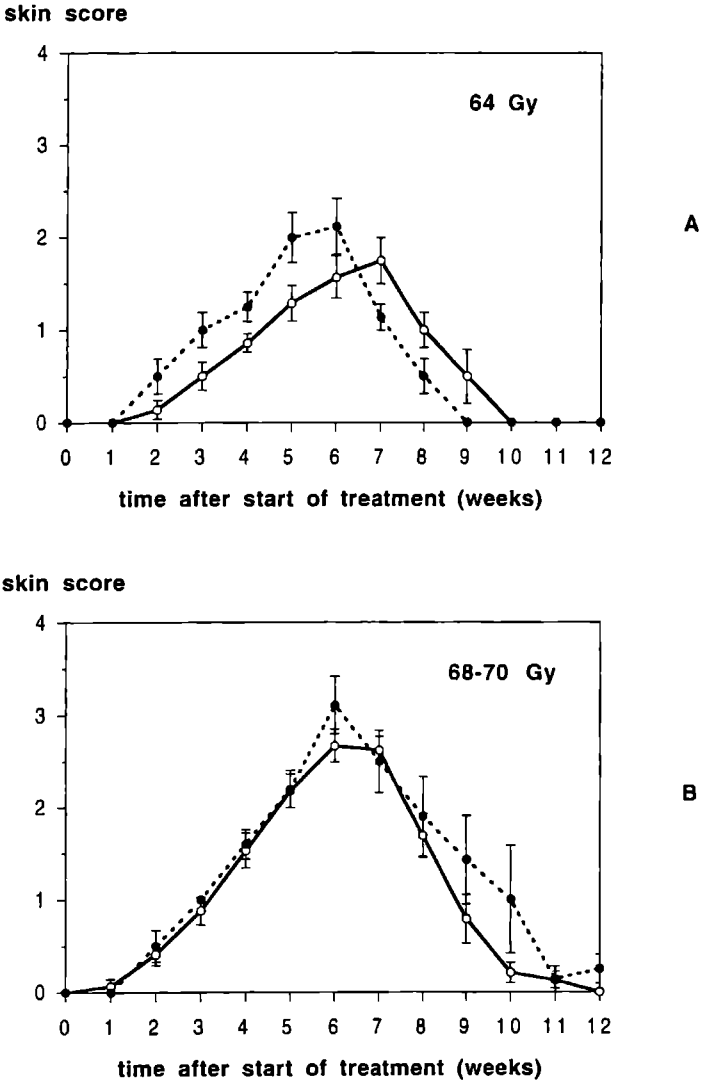


Fig. 2. *Average skin score during and after treatment. Treatment starts at "week 0". Open symbols represent conventional fractionation, closed symbols represent accelerated fractionation. Vertical bars indicate standard error of the mean. Fig. 2A includes patients irradiated to a dose of 64 Gy. Fig. 2B includes patients irradiated to a dose of 68 or 70 Gy.*

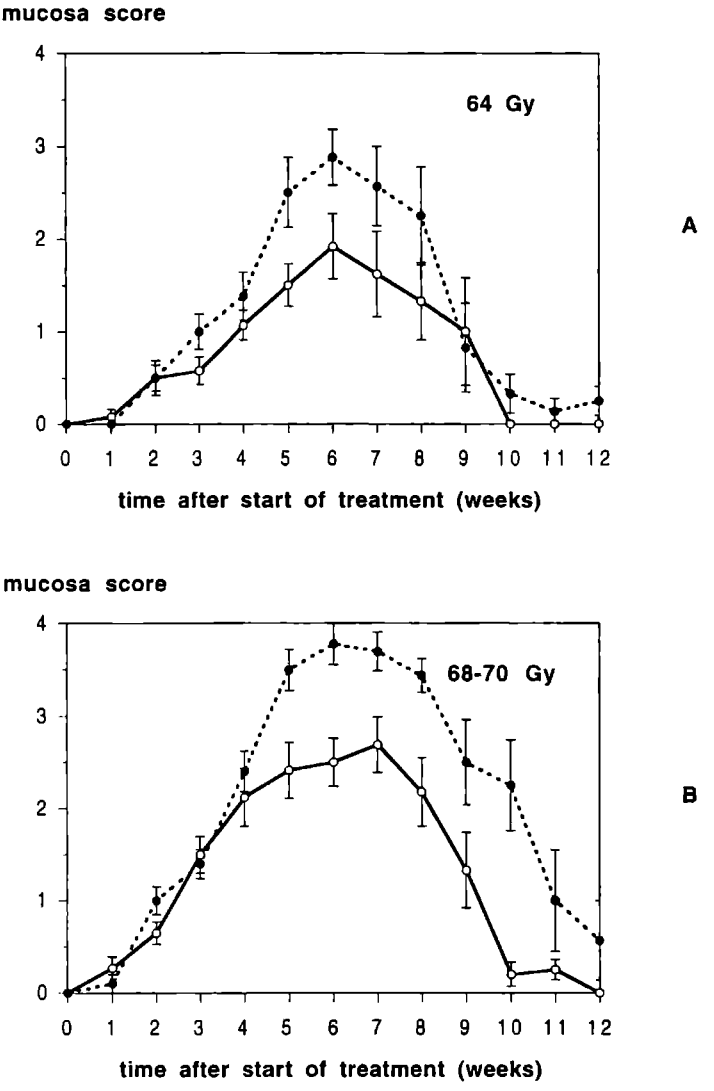


Fig. 3. *Average mucosal score during and after treatment. Treatment starts at "week 0". Open symbols represent conventional fractionation, closed symbols represent accelerated fractionation. Vertical bars indicate standard error of the mean. Fig. 3A includes patients irradiated to a dose of 64 Gy. Fig. 3B includes patients irradiated to a dose of 68 or 70 Gy.*

with spotted or confluent mucositis is given in Table 3. With a total dose of 64 Gy, spotted mucositis developed more often in the AF-group while confluent mucositis was rare in both groups. In the 68-70 Gy dose groups, most patients in both groups developed spotted mucositis. The incidence of confluent mucositis was significantly higher in the AF-group. The average time at which confluent mucositis was reached was day 34 in the CF-group and this reaction level was maintained for an average of 26 days. In the AF-group confluent mucositis was reached on day 38 and persisted for 24 days. Again, complete healing occurred within 3 months in all cases.

Dysphagia: The need for medication against dysphagia in the different treatment groups is shown in Table 3. Tube feeding and hospitalization for a period of 1 week was needed for one patient in the AF-group (stage T_2N_0, total dose 68 Gy). No patients in the CF-group required nutritional support of this kind.

For the endpoints skin score ≥ 3 and mucosa score = 4, dose response curves were constructed using probit analysis (Fig. 4). The ED_{50} for confluent mucositis was 69 Gy in the CF-group and 66 Gy in the AF-group, which is a statistically significant difference ($p < 0.05$). Assuming that repopulation accounts for this 3 Gy difference, a mean recovery of 0.3 Gy per day can be derived for the laryngeal mucosa. The ED_{50} for skin reaction showed no significant difference for the two treatment modalities.

Late toxicity

Severe late effects were observed only in those patients treated up to a total dose of 68 or 70 Gy either by conventional or accelerated fractionation. In the AF-group, four of 10 patients developed severe edema of the laryngeal mucosa. In three patients it appeared 2 to 7 months after completion of treatment and regressed spontaneously within 6 months without causing serious discomfort. In one of these patients there was also a small area with transient mucosal ulceration on the false cord. This defect healed spontaneously within 5 months. One patient was seen with severe edema directly after completion of the course of irradiation which, 3 months later, was accompanied by necrosis of cartilage requiring total laryngectomy. No tumor was found in the specimen. After conventional fractionation radiotherapy, severe edema was observed in four of 24 patients. In three cases this was observed 3 to 5 months after completion of the treatment. Spontaneous regression occurred within 6 months. One patient developed severe edema after 2 years of follow-up, persisting at the moment this report was written. We have no evidence of recurrent tumor in this patient so far.

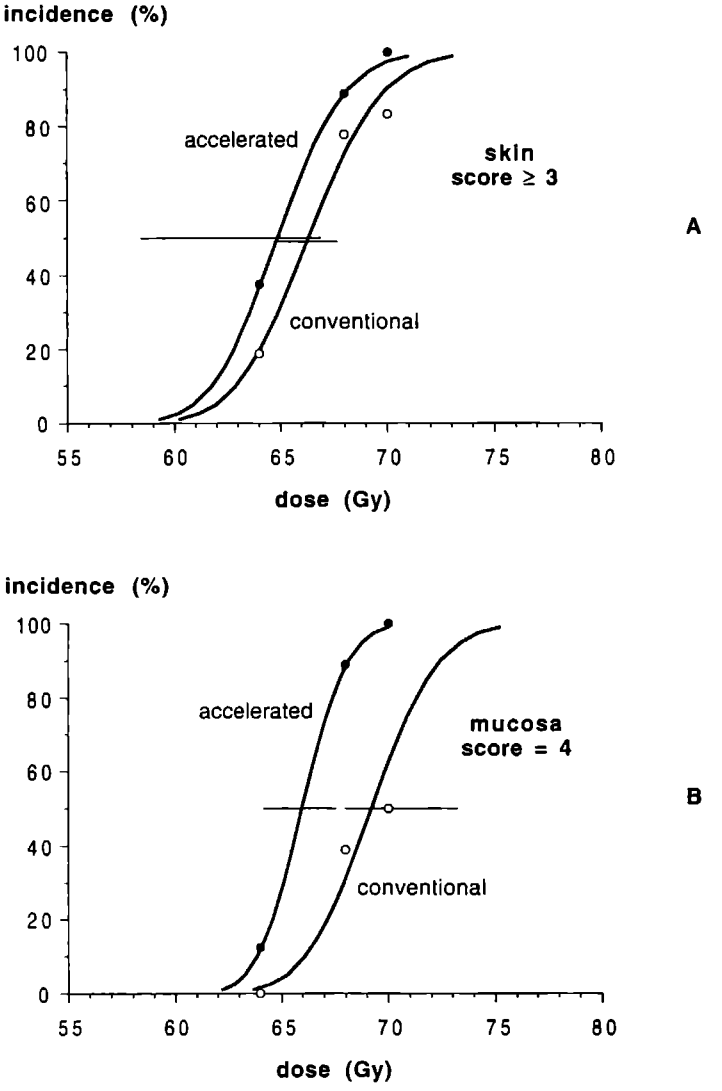


Fig. 4. *Dose response curves for skin score ≥ 3 (A) and mucosa score = 4 (B) constructed by probit analysis. Closed and open symbols represent datapoints of the accelerated and conventional schedules respectively. Horizontal bars represent 95% confidence limits.*

Although it did not reach the level of statistical significance (Spearman's correlation test, $p = 0.09$), it is of interest to note that there was the indication of a correlation between the severity of acute mucosal reactions and laryngeal edema, irrespective of total dose delivered, suggesting these late effects to be "consequential" to acute effects and not of independent origin. All patients treated with accelerated fractionation that developed confluent mucositis in the acute phase also showed some degree of edema of the laryngeal mucosa some time in follow-up. Those patients whose peak mucositis score was 3 or less never developed any laryngeal edema.

No severe late skin reactions were reported in any of the patients.

Discussion

To study the influence of different irradiation parameters such as total dose, dose per fraction and overall treatment time, one should alter only one of these parameters at a time. We chose to study moderate reduction of overall treatment time in order to leave total dose and dose per fraction unchanged. All previously reported schedules for accelerated fractionation in head and neck cancer reduced the total dose or dose per fraction (< 2 Gy) or both to accomplish sufficient reduction of overall treatment time. Mostly patients with advanced carcinoma of the head and neck were studied, regardless of site of origin of the tumor. We believe that the biological properties of tumors differ with their site of origin. Also side-effects of irradiation are obviously related to the site of the tumor and the area treated. We therefore elected to study a well defined, homogeneous population, that is, patients with laryngeal cancer.

We used a concomitant boost type fractionation schedule with the acceleration of the treatment taking place at the end of the treatment series. With a schedule like this the acute reactions will be postponed to the end of the treatment period, thereby lowering the risk of interruption of the treatment for this reason. Available radiobiological and clinical data incorporated in mathematical models point towards concomitant boost schemes as being potentially the most successful in terms of tumor control [14, 17]. The role of proliferation as an important factor in tissue recovery after radiation, not only in tumors but also in normal tissues, is widely recognized [5]. It is therefore not surprising that we observed more severe acute reactions, especially mucosal reactions, with accelerated fractionation. As expected, there was no difference during the first 4 weeks of treatment since acceleration in the AF-group was not started until the fourth week.

Ang et al. showed that repopulation in mouse lip mucosa increases during the first 10 days after the initial dose of radiation [2]. They calculated that, between the 7th and 10th day, repopulation accounts for about 1.0 Gy of recovery per day. From our material we calculated a mean recovery of 0.3 Gy per day for laryngeal mucosa over the entire treatment period. This could indicate a higher potential for repopulation in mouse than in man as suggested by Dörr et al. [3]. The comparison however is hampered by different definitions of endpoints. Van der Schueren et al. studied mucosal and skin reactions in patients treated by different fractionation regimens [18]. They observed confluent mucositis in all patients treated up to 70 Gy by conventional fractionation radiotherapy. The average time at which this reaction level was reached was day 22 and it persisted for about 5 weeks. They suggested a threshold for confluent mucositis of approximately 20 Gy when given in fractions of 1.6-2 Gy which then would become apparent 9 days after delivery of this dose. In the present study we observed a lower incidence of confluent mucositis (42%) in patients treated to a comparable dose level by conventional fractionation. This reaction level was also reached later (day 34) which is 20 days after the point at which 20 Gy had been administered. We thus find a lower incidence and a slower development of confluent mucositis in our material. Van der Schueren et al. studied patients with advanced head and neck tumors and it is conceivable that treatment volumes were larger in their patients, including more of the oropharyngeal and oral mucosa. Possibly also the general condition of these patients was poor due to their large tumors. This indicates that mucosal reaction patterns do not only depend on dose and fractionation schedule. Factors such as irradiated mucosal surface, sites treated and general condition of the patient may also play an important role.

A study on concomitant boost radiotherapy in nasopharyngeal and oropharyngeal cancer was conducted at the MD Anderson Cancer Center [1]. Initially patients were randomized over three different treatment-arms. The boost was either given twice a week during the 5 to 6 weeks of the basic treatment course (arm 1), or every day during the first 2-2.5 weeks (arm 2) or during the last 2-2.5 weeks (arm 3). Later arms 1 and 2 were dropped because the tumor control rate of arm 3 appeared to be superior and it was logistically the most convenient schedule. Arm 3 is comparable to our fractionation scheme. Daily fractions of 1.8 Gy, five times a week were given for 6 weeks. The boost consisted of 10 to 12 fractions of 1.5 Gy. Thus, total dose ranged between 69 Gy and 72 Gy given in 6 weeks. In this treatment group 35 of 43 patients (81%) developed confluent mucositis. This is comparable with the incidence of confluent mucositis that we found in our study in those patients that were treated to a total dose of 68 or 70 Gy (9/10 or 90%). In five of 43 patients they observed mucositis lasting 6 weeks or longer after completion of treatment. In our

experience mucositis had always disappeared at this point Irradiated mucosal surface and site treated might bring about this difference

In the MD Anderson study as well as in the present study, the overall treatment time was reduced without reduction of total dose Further shortening of treatment time, as tested by Lamb et al in patients with advanced head and neck cancer [9], requires adjustment of the total dose to prevent excessive mucosal reactions They delivered three fractions of 1 8 Gy, 4 h apart, on 3 treatment days per week (Monday, Wednesday, Friday) to a total dose of 59 4 Gy delivered in 33 fractions over 24-25 days With this regimen they observed severe acute mucosal reactions with haemorrhagic mucositis in some patients and 52% of patients required hospital admission

Peracchia et al drastically reduced the treatment time to 9-11 days and delivered a dose of 48-54 Gy by three times a day fractionation [13] The dose per fraction was 2 Gy with an interval between fractions of at least 3 h Persistent confluent mucositis occurred in all patients, leading to necrosis in 68% of patients On the contrary, acceptable acute toxicity was reported by Olmi et al using an almost identical schedule [12] 48-52 Gy were administered over a total time of 11-12 days, three times a day 2 Gy with a 4 h gap between each session By reducing dose per fraction to 1 5 Gy and increasing the interval between fractions to 6 h, Saunders et al managed to deliver 54 Gy in 12 consecutive days [15] Acute mucosal reactions were reported to be troublesome but tolerable They demonstrated that extremely short schedules are feasible but require adjustment not only of total dose but also of dose per fraction

Severe laryngeal edema was seen somewhat more often in those patients treated by the accelerated scheme to a dose of 68-70 Gy four of 10 versus four of 24 in the CF-group This edema was transient in all but one case in which it was accompanied by necrosis of cartilage necessitating laryngectomy This patient continued heavy smoking and drinking during and after radiotherapy

Of interest is a possible correlation between acute mucosal reactions and later onset of laryngeal edema Our patient numbers in this study however may be too small to confirm this relationship and we are currently investigating a larger group of patients If indeed laryngeal edema proves to be related to severe acute mucosal reactions irrespective of total dose and fractionation schedule, one might consider this a "consequential late effect" as defined by Peters et al [14] The side-effects observed by Perrachia et al in their study on accelerated fractionation for head and neck cancer are a typical example of this phenomenon non-healing mucositis leading to necrosis after 4-5 months [13] Also Olmi et al observed a high incidence (24%) of severe late damage but they found no relationship between acute and late sequelae [12]

Most other investigators do not report significant increase of late toxicity after moderate reduction of overall treatment time [1, 9, 20]. The schedule used in Mount Vernon Hospital resulted in late toxicity of skin and mucosa comparable to that of conventional radiotherapy [10]. However, they also report a trend towards more pallor and telangiectasia in patients where early mucosal reactions took longest to heal. Recovery of hair loss and salivary gland function was even better after accelerated fractionation, possibly due to the lower total dose that was delivered with this regimen.

Since the availability of high energy photons, skin reactions are usually not dose limiting anymore. There was an increased incidence of moist desquamation in our patients treated by accelerated fractionation and to a total dose of 68-70 Gy. However, it is our experience and of others [1, 9, 18] that these reactions are relatively easy to overcome and have less functional impact than mucosal reactions.

Increased acute toxicity is associated with all schedules of accelerated fractionation as is confirmed by this study. With moderate reduction of the overall treatment time by 11 days acute reactions remain tolerable although one should be aware of the potential hazard of consequential late damage. Further shortening of treatment time is not feasible without adjustment of other irradiation parameters such as total dose and dose per fraction.

References

1 Ang, K K , Peters, L J , Weber, R S et al Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx Int J Radiat Oncol Biol Phys 19 1339-1345, 1990

2 Ang, K K , Xu, F-X , Vanuytsel, L and Van der Schueren, E Repopulation kinetics in irradiated mouse lip mucosa the relative importance of treatment protraction and time distribution of irradiations Radiat Res 101 162-169, 1985

3 Dori, W and Kummermehr, J Accelerated repopulation of mouse tongue epithelium during fractionated irradiations or following single doses Radiother Oncol 17 249-259, 1990

4 Fowler, J F Intervals between multiple fractions per day Differences between early and late radiation reactions Acta Oncol 27 181-183, 1988

5 Hall, E J Time, dose and fractionation in radiotherapy In Radiobiology for the radiologist 3rd edition, pp 239-259 Editor Hall, E J J B Lippincott Co, Philadelphia, PA, 1988

6 International Commission on Radiation Units and measurements Dose specification for reporting external beam therapy with photons and electrons Report 29 ICRU Publications, Washington, DC, 1978

7 International Union Against Cancer TNM classification of malignant tumours 4th edition Springer-Verlag, Berlin, 1987

8 Knee, R , Fields, R S and Peters, L J Concomitant boost radiotherapy for advanced squamous cell carcinoma of the head and neck Radiother Oncol 4 1-7, 1985

9 Lamb, D S , Spry, N A , Gray, A J , Johnson, A D , Alexander, S R and Dally, M J Accelerated fractionation radiotherapy for advanced head and neck cancer Radiother Oncol 18 107-116, 1990

10 Lartigeau, E , Saunders, M I , Dische, S , Warburton, M F and Des Rochers, C A Comparison of the late radiation changes after three schedules of radiotherapy Radiother Oncol 20 139-148, 1991

11. Maciejewski, B., Withers, H.R., Taylor, J.M.G. and Hliniak, A. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx; tumor dose-response and repopulation. Int. J. Radiat. Oncol. Biol. Phys. 16: 831-843, 1989.

12. Olmi, P., Cellai, E., Chiavacci, A. and Fallai, C. Accelerated fractionation in advanced head and neck cancer: results and analysis of late sequelae. Radiother. Oncol. 17: 199-207, 1990.

13. Peracchia, G. and Salti, C. Radiotherapy with thrice-a-day fractionation in a short overall time: clinical experiences. Int. J. Radiat. Oncol. Biol. Phys. 7: 99-104, 1981.

14. Peters, L.J., Ang, K.K. and Thames, H.D. Accelerated fractionation in the radiation treatment of head and neck cancer. A critical comparison of different strategies. Acta Oncol. 27: 185-194, 1988.

15. Saunders, M.I., Dische, S., Fowler, J.F. et al. Radiotherapy employing three fractions on each of twelve consecutive days. Acta Oncol. 27: 163-167, 1988.

16. Thames, H.D., Peters, L.J., Withers, H.R. and Fletcher, G.H. Accelerated fractionation vs. hyperfractionation: rationales for several treatments per day. Int. J. Radiat. Oncol. Biol. Phys. 9: 127-138, 1983.

17. Tucker, S.L. and Chan, K. The selection of patients for accelerated radiotherapy on the basis of tumor growth kinetics and intrinsic radiosensitivity. Radiother. Oncol. 18: 197-211, 1990.

18. Van der Schueren, E., Van den Bogaert, W., Vanuytsel, L. and Van Limbergen, E. Radiotherapy by multiple fractions per day (MFD) in head and neck cancer: acute reactions of skin and mucosa. Int. J. Radiat. Oncol. Biol. Phys. 19: 301-311, 1990.

19. Wang, C.C. The enigma of accelerated hyperfractionated radiation therapy for head and neck cancer. Int. J. Radiat. Oncol. Biol. Phys. 14: 209-210, 1988.

20. Wang, C.C., Blitzer, P.H. and Suit, H.D. Twice-a-day radiation therapy for cancer of the head and neck. Cancer 55: 2100-2104, 1985.

21. Withers, H.R. Biologic basis for alterated fractionation schemes. Cancer 55: 2086-2095, 1985.

22. Withers, H.R., Taylor, J.M.G. and Maciejewski, B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol. 27: 131-146, 1988.

CHAPTER 3

ALTERED FRACTIONATION: LIMITED BY MUCOSAL REACTIONS?

Johannes H.A.M. Kaanders

Albert J. van der Kogel

K. Kian Ang

Radiother. Oncol., accepted

Abstract

The effectiveness of accelerated fractionation and hyperfractionation in cancer of the head and neck has been confirmed in randomized studies These new fractionation strategies are almost invariably accompanied by an increase of early normal tissue reactions, in particular mucosal reactions This paper presents a survey of the available experimental and clinical mucositis data and aims to assess as to what extent the upper aerodigestive tract mucosa is limiting to treatment intensification by altered fractionation

The rate of dose delivery is the most important determinant for early radiation reactions With accelerated radiotherapy, relative to a conventional treatment of 7 weeks, the maximum achievable gain in treatment time is 2 weeks with the mucosa being the limiting tissue Any further acceleration requires a reduction of dose Manipulations with the temporal distribution of dose, fraction dose, and optimization of interfraction intervals can improve tolerance but probably do not allow significant further intensification of the existing accelerated schedules Dose escalation by hyperfractionation does not seem to be directly limited by early mucosal reactions Late reacting tissues are more likely to limit intensification of these schedules

Suggestions for further improvement of treatment outcome include generation of a potent agent which can ameliorate radiation mucositis and so permit further intensification of radiotherapy schedules, combination of altered fractionation schedules with hypoxic modifiers, and tailoring of the treatment strategy based on patient and tumor characteristics

Introduction

Altered fractionation schedules as means to improve radiation treatment outcome have been the subject of extensive clinical testing, especially during the last decade Now, randomized studies have confirmed the effectiveness of accelerated fractionation and hyperfractionation in some cancer sites of the head and neck area [2, 16, 20, 39, 40, 65] These new fractionation schedules were designed to enhance the therapeutic ratio by improving tumor control without increasing late toxicity Hyperfractionation exploits the difference in the fractionation sensitivity between rapidly and slowly renewing tissues, i e a higher total dose can be given when the dose per fraction is reduced With accelerated fractionation the radiation dose is delivered in reduced overall treatment time by giving multiple fractions per day Provided that sufficient time between the fractions is allowed for repair of sublethal damage to approach completion, no or only marginal increase of late morbidity is expected But what about acute reactions? Already in 1932 it was Coutard who, based on clinical observation and logic reasoning, stated "An observation of the facts leads us to admit that the radiosensitivity of cancer cells of epidermal origin is usually of the same degree as the radiosensitivity of the germinal cells of the epidermis" [14] In fact, this became his guidance for dosing individual patients Consistent with this principle and not surprisingly, the new fractionation strategies are almost invariably accompanied by an increase of early normal tissue reactions, in particular mucosal reactions

The purpose of this paper is to review the available experimental and clinical mucositis data and to assess as to what extent the upper aerodigestive tract mucosa is limiting to treatment intensification by altered fractionation

Assessing and reporting mucosal reactions

Before reviewing the data from the literature it is important to emphasize some aspects that are essential for adequate assessment and useful reporting of mucosal reaction patterns

First of all endpoints should be clearly defined It is not uncommon that in scientific papers descriptions such as "brisk" or "severe mucositis" are used without further details Mere use of the term "mucositis" insufficiently describes the condition that is being looked at A further specification is required, e g "confluent mucositis" indicating that confluent pseudomembranes were observed, if possible with an indication of the relative mucosal surface affected The use of composite scales is discouraged These scales combine multiple elements of tissue reactions, sometimes both objective and subjective, into one composite

score. The interpretation of such scores is difficult and it complicates the understanding of mechanisms behind the acute tissue responses. The frequency of radiation side-effects should be expressed quantitatively, avoiding terms as "most", "common" or "some" which, unfortunately, are still often used.

Another aspect is the difference of reaction patterns by head and neck subsite. This too was already described by Coutard in his paper of 1932 [14] but is still very often ignored. Fig. 1 compares the incidence of confluent mucositis in larynx and oropharynx. We treated patients with a conventional schedule to a dose of 68 Gy in fractions of 2 Gy over 7 weeks. The mucosal reactions were observed weekly during and after the treatment until healing was complete. Confluent mucositis was more frequently observed in the oropharynx. A similar observation was made by Denham et al. comparing hypopharynx and oropharynx [19]. It is not clear whether these differences by site persist with intensified treatments. In this paper we can only consider the upper aerodigestive tract mucosa in general because of a lack of sufficiently detailed data for subsites.

When is mucositis to be considered as severe and when do mucosal reactions become limiting to further treatment intensification? Obviously, the highest grade on the objective scoring scale is an indicator but definitely not the only one and probably also not the best

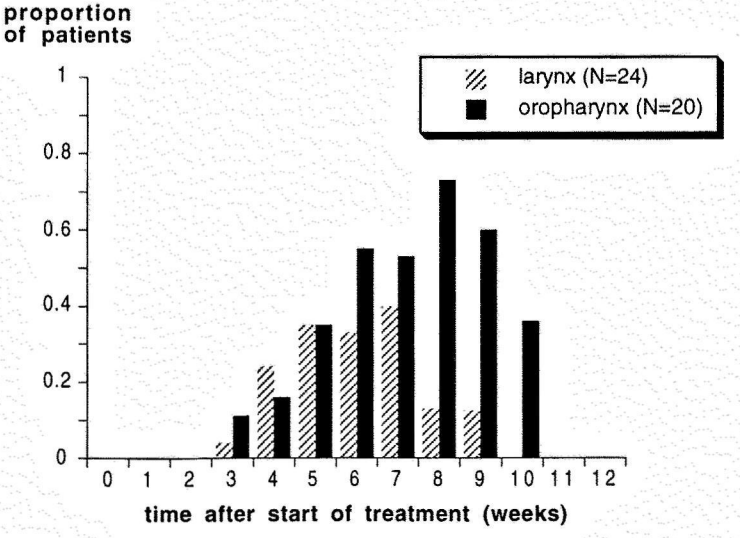


Fig. 1. *Proportion of patients with confluent mucositis during and after conventional radiotherapy comparing larynx and oropharynx.*

one. Some scales have "confluent mucositis" as the highest grade but others include "ulceration" or "necrosis" as an even higher level of damage. The latter however is rare as an early event. Confluent mucositis is observed frequently, also with conventional treatment (Fig. 1). Acceleration of treatment produces confluent mucositis in the great majority of patients. Despite this high incidence of confluent mucositis with altered fractionation, most schedules are considered as acceptable with regard to acute toxicity. This is because the mucosa generally heals within a reasonable period of time and without significant consequential late effects. The duration and completeness of the healing process in fact determine whether the limits of tolerance are being reached. Confluent mucositis represents a certain level of cellular depletion of the mucosal lining. It was suggested by van der Schueren et al. that, in the human oral mucosa, a threshold dose of 20 Gy is needed to cause confluent mucositis [81]. In their clinical experiments, further increase of the radiation dose directly influenced the duration of mucositis. The time that is required for healing very likely reflects the degree of mucosal stem cell kill. If there is (nearly) complete depletion of stem cells in a certain area, regeneration depends on proliferation and migration from the edges of the lesion. The larger the affected area the more time will be needed for complete recovery and the higher the risk of persistent, consequential damage. Fig. 2 illustrates how increased levels of damage are expressed as prolonged duration of mucosal reactions. The figure presents data from a toxicity study of accelerated fractionation combined with carbogen and nicotinamide as modifiers of hypoxia in patients with larynx- and hypopharynx carcinomas [46, 47]. A total dose of 64-68 Gy was delivered in 2 Gy fractions over a 5-5.5 week period. The overall treatment time was moderately reduced by delivering two fractions per day during the last one and a half week of the radiation course. The interval between fractions was at least 6 h and the dose per fraction 2 Gy. Carbogen and nicotinamide were added in consecutive phases of the study. With acceleration alone 90% of patients developed confluent mucositis. Further enhancement by carbogen and nicotinamide was reflected by prolonged healing times.

Other indicators of the severity of mucosal reactions can be dysphagia, use of analgetics, weight loss, tube feeding and hospitalization. To a large degree these are subjective parameters and dependent on local and individual treatment policies. For example, in some institutes there is a tendency to perform a percutaneous gastrostomy earlier in the treatment to prevent excessive weight loss. Also, when multiple fractions per day are given, patients are often hospitalized but it is not always reported whether this was because of severe side-effects or just because of logistic reasons. These parameters obviously are important indicators of the patients' well being. However, they do not very accurately reflect the biological effects of radiation.

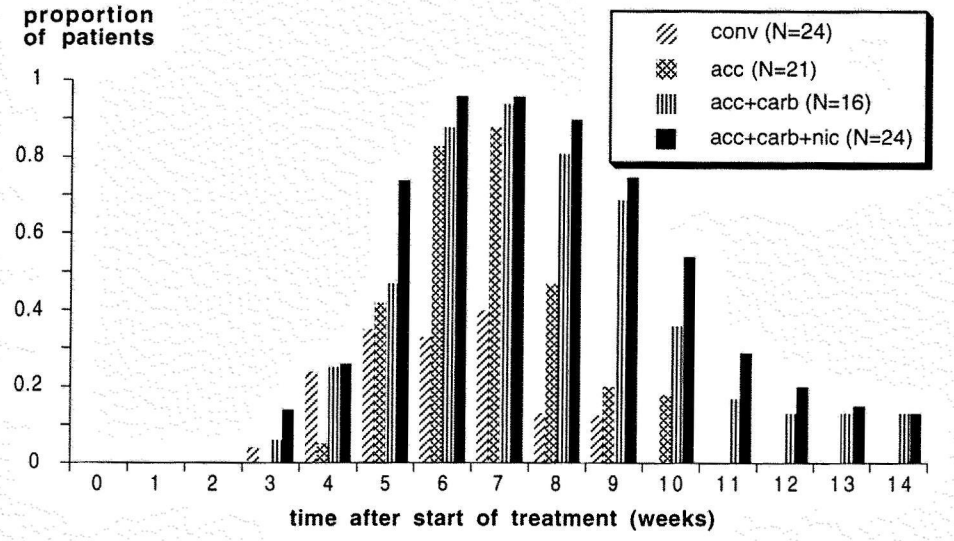


Fig. 2. *Proportion of patients with confluent mucositis during and after radiotherapy comparing conventional radiotherapy (conv), accelerated radiotherapy (acc), accelerated radiotherapy with carbogen (acc+carb), and accelerated radiotherapy with carbogen and nicotinamide (acc+carb+nic).*

Even when only objective endpoints are used it is difficult to compare studies because of the differences in patient selection and tumor characteristics and inter-observer variations. For example, the concomitant boost schedule developed at the MD Anderson Cancer Center produces grade 3-4 (RTOG-scale) mucositis in 94-100% of the patients according to the publications from this center [36, 55]. However, when tested in a multicenter study the same schedule was reported to give only a 47% incidence of grade 3-4 reactions [31].

Finally, decisions as to whether radiation reactions are tolerable or not and if a particular treatment schedule should be modified are highly dependent on physician experience and philosophies. At centers where there is a large experience with intensified treatments and where there are well developed supportive care programs, one may be willing to accept greater acute toxicity than in some other centers.

Fractionation parameters: studies in mouse and human mucosa

Experimental studies on the upper aerodigestive tract mucosa have been performed on mouse lip and tongue Fractionation experiments covering a wide range of fraction sizes from 1 2 to 22 5 Gy as well as continuous and fractionated low dose rate and high dose rate experiments demonstrated characteristics typical for acutely responding tissues with α/β ratio s in the range of 5 8 to 16 4 Gy [1, 3, 24, 72, 73] It also became clear from these data that reducing the dose per fraction below 2 Gy does not lead to a further increase in tolerance [1] Fractionation parameters of human normal tissues are generally obtained by retrospective analysis An exception is the clinical study by Denham et al [18] They treated patients with incurable head and neck cancers with fractionated radiotherapy using dose rates varying from 0 8 to 240 Gy/h For the human oropharyngeal mucosa they calculated an α/β ratio of 9 3 Gy (5 8-17 9, 95% CI) with patchy mucositis as the endpoint This corresponds well with the values found in mouse studies From these same data they derived a very short half-time for repair of sublethal damage ($T_{1/2}$) of 15 min (8 4-90, 95% CI) The mouse data indicate somewhat longer repair half-times in the range of 37-72 min [3, 24, 72] A recent study on mouse lip mucosa suggested a bi-exponential repair process with a long $T_{1/2}$ of 150 min and a fast component of 27 min but with a large proportion (82%) of the damage being repaired by the fast component [73] Repair processes for these acute reactions can thus be considered to approach completion after 4-5 h However, there are clinical studies suggesting differently These studies have been reviewed by Bentzen et al [8] and include the RTOG studies 7913 and 8313 [15, 57], a study from the MD Anderson Cancer Center [32], and a study from the Center of Oncology in Warsaw [13] All four studies showed a decrease in the incidence of mucosal reactions when the interval between fractions given on a same day was increased, typically from around 4 h to around 6 h The investigators compared the steepness of the dose-response curves from studies not involving incomplete repair with those derived from the above four studies It was shown from this comparison that $T_{1/2}$ for human mucosa must be in the range of 2 to 4 h, i e longer than the values for mouse mucosa and much longer than the value derived by Denham et al although, admittedly, the corresponding 95% confidence intervals of the latter were fairly large (8 4-90 min) On the other hand, to our knowledge, this is the only clinical study specifically designed to address the question of repair kinetics Retrospective analysis of data from different clinical studies is flawed by many confounding factors Additional human data will be needed to resolve this issue

The repopulation kinetics of the mouse mucosa have been studied by Ang et al [4] and by Dorr et al [25, 26] A substantial repopulation effect was observed after a lag time of

about 3 days from the start of treatment. This regenerative response increases progressively and accounts for about 1 Gy per day worth of recovery between days 7 and 10 in mouse lip [4]. Dörr et al. demonstrated that in mouse tongue epithelium repopulation can fully counteract the effect of five weekly doses of 2.5-3.5 Gy during week 2 and 3 of a course of daily fractionated irradiation [25, 26]. Another important finding was that the rate of repopulation depended on the level of damage. The endpoint in the study by Ang et al. was spotted mucositis, whereas that of Dörr et al. was complete denudation. This might explain the higher repopulation rates found by the latter group.

Both investigators also addressed the issue of protraction and temporal distribution of radiation fractions. In mouse lip experiments 10 fractions were administered in 3 days (multiple fractions per day) or in 11 days (daily fractions) [4]. This led to a gain of about 13 Gy for peak mucosal reactions, i.e. 1.6 Gy per day. When the same 10 fractions were administered in two short courses of five fractions given in 1.5 days with a rest period of 8 days (overall time 11 days), an additional 5 Gy was recovered. This suggests that repopulation may be more efficient during a treatment-free period. Dörr [23] simulated split-course treatments by delayed top-up doses following daily fractionated irradiation, thus introducing splits of 6 h to 13 days. He demonstrated that the rate of repopulation rapidly increases during fractionated radiotherapy but decelerates after cessation of treatment and suggested that it is the greater initial damage that stimulates more efficient repopulation.

Data from Fletcher et al. indicate that human oropharyngeal mucosa can counteract the full daily dose at the end of a conventional course of radiation [29, 78]. Twenty patients were treated to doses of 55 Gy in 4-4.5 weeks with fraction sizes of 2.45-2.75 Gy. Three of them showed signs of mucosal healing during the last week of treatment. When the same dose was administered in 5-5.5 weeks (2-2.2 Gy daily dose) healing had begun in two of 11 patients before completion of treatment. Further reduction of the daily dose to 1.83-2 Gy and protraction to 6-6.5 weeks allowed healing of the mucosa in six of eight patients during the final stages of treatment. These data suggest that human oropharyngeal mucosa can counteract about 1.8 Gy per day at the end of a 6-week course of irradiation.

Van der Schueren et al. investigated the influence of multiple fractions per day and treatment gaps on mucosal proliferation in man [81]. In patients with advanced head and neck cancers conventional schedules to doses of 50 and 70 Gy were compared to split-course schedules with three or four fractions daily. The fraction sizes used were 1.6 or 2 Gy, overall treatment time was 4 to 7 weeks, and the total dose ranged from 60 to 67.2 Gy. The most important parameter that was modified was the dose given in one treatment series. The first schedule consisted of two unequal radiation series: 48 Gy in 12 days, followed by a second series of 19.2 Gy in 4 days after a 3-4 week interval. The

subsequent treatment schedules were divided in equal series: two times 30 Gy, three times 22.4 Gy, and four times 16 Gy, all with 2 week intervals. The mucosal reactions were scored three or four times per week and with the last schedule (four times 16 Gy) even daily because of the short duration of reactions. The treatment-free intervals were long enough to allow for (nearly) complete healing between series. This, and the frequency of scoring gave detailed information allowing analysis of the mucosal reaction patterns for each of the series within these various split-course schedules. The investigators observed a linear relationship between the duration of spotted and/or confluent mucositis and the dose given per treatment series. This supports the notion that the healing time is a good indicator of the level of radiation damage at the tissue level. It was demonstrated that the duration of mucositis with conventional treatment to 50 Gy was about 5 days longer than would be expected with a split-course treatment of the same total dose. The most unusual schedule delivered 16 Gy in eight fractions over 2 days, repeated four times with 12 days intervals. Thus a total dose of 64 Gy was delivered in 6 weeks. With this schedule the majority of patients did not transgress the level of spotted mucositis and the duration of reactions was very short. There were 18 fully evaluable "reaction cycles" where the patients were scored at least six times a week during the full reaction period. Only once in one patient a 2-day period of confluent mucositis was observed.

Thus, both animal and human data indicate that discontinuous irradiation without increasing the total length of radiotherapy can allow for a more effective regeneration of the mucosa. However, such discontinuous irradiation may also have consequences for tumor response.

In summary we have learned the following from studying mucosal reaction patterns in animals and patients: 1) The α/β value for mucositis is in the range of what can be expected for acutely responding tissues (5.8-16.4 Gy), but reduction of fraction dose below 2 Gy may not lead to further tissue sparing. 2) Short $T_{1/2}$ values have been derived from animal experiments (37-72 min) and one clinical study (15 min) but retrospective analysis of other clinical data suggests longer $T_{1/2}$ values. 3) The rate of repopulation increases progressively from the third day (in mice) of treatment and can counteract daily doses of about 1.8 Gy in man and up to 3.5 Gy in mice. 4) The rate of repopulation depends on the level of damage which may explain a more effective regeneration with discontinuous schedules with intensified dose delivery at the beginning of treatment.

Clinical studies on accelerated and hyperfractionated radiotherapy in head and neck cancer

A search of the international English literature over the past 25 years revealed 62 different schedules of accelerated and/or hyperfractionated radiotherapy which have been tested for definitive treatment of head and neck tumors. We have categorized these schedules into four groups: A) accelerated fractionation with moderate reduction of overall treatment time (33-40 days) and unchanged total dose; B) accelerated fractionation with overall treatment time < 33 days but > 17 days, usually with moderate reduction of total dose; C) accelerated fractionation with overall treatment time ≤ 17 days and reduction of total dose; and D) hyperfractionation. This grouping was done merely to bring some order in this large number of studies and because treatment time appears to be the major determinant for

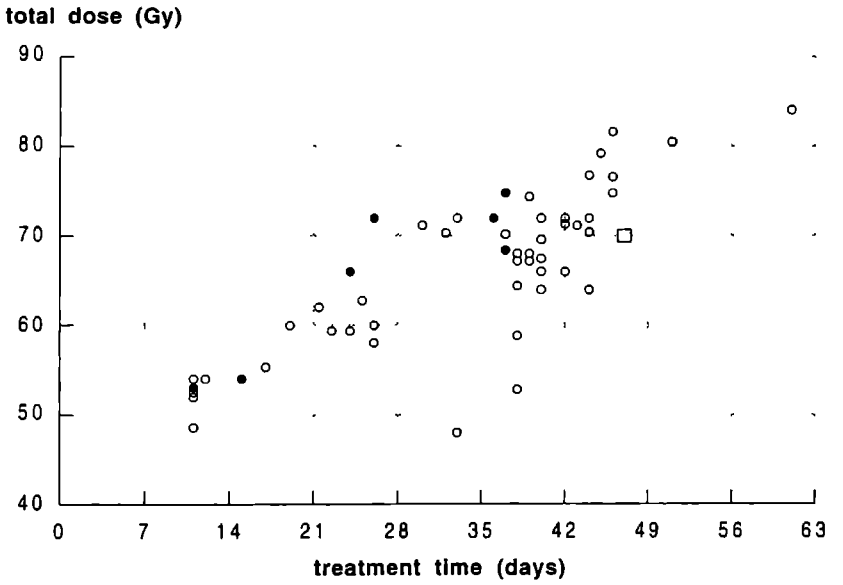


Fig. 3. *Schedules of altered fractionation tested in the head and neck area, plotted as a function of total dose and overall treatment time [5, 6, 10, 11, 13, 15-17, 19-22, 32, 34-37, 39-44, 47-50, 52-55, 57, 58, 60-63, 65-70, 74, 75, 77, 80-83]. Open square represents conventional treatment. Open circles represent schedules with acceptable mucosal morbidity. Closed circles represent schedules that were abandoned or modified because of excessive early mucosal toxicity.*

mucosal reactions. Each schedule has been interpreted with regard to acute mucosal toxicity according to the investigators' conclusions and categorized as "acceptable" or "severe mucosal morbidity requiring modification of the treatment schedule". Fig. 3 shows a scattergram of various schedules plotted as a function of total dose and overall time. Studies which combined radiotherapy with chemotherapy or surgery were excluded as well as papers without sufficient data on acute mucosal toxicity. If available, the median or mean values of actual delivered dose and overall treatment time are presented. Many papers however do not provide these data in which case the prescribed dose and time are used.

A) Accelerated fractionation with moderate reduction of overall treatment time (33-40 days) and unchanged total dose. This group includes four types of schedules: split-course: treatment is given twice or three times daily for 1-2 weeks followed by a rest period of 2-4 weeks after which treatment is resumed; concomitant boost type schedules, giving the boost as a second daily fraction during part of the treatment, usually at the end; schedules which increase the weekly dose rate by treating during weekends; and schedules which increase the weekly dose rate by giving twice daily treatments continuously with small fraction size. We identified three schedules for which modification was recommended because of severe acute mucosal toxicity [17, 37, 54]. The schedules discussed in this section are diagrammatically represented in Fig. 4.

Maciejewski et al. reported their experience with a schedule of pure acceleration, i.e. only reduction of the overall treatment time without change of the total dose or dose per fraction [54]. This was accomplished by giving single daily fractions of 2 Gy for 7 days a week over 5 weeks which allowed "ideal" interfraction intervals of 24 h between all fractions. They reported severe mucosal reactions (score > 15, composite scale) lasting longer than 3 weeks in 48% of the patients. Soft tissue necrosis in the oral cavity or oropharynx occurred in 21% of the patients within 7-12 weeks after the completion of the treatment which they considered to be consequential to the severe early reactions. Because of unacceptable toxicity dose per fraction was reduced to 1.8 Gy. Toxicity data of this modified schedule are not yet available.

Another schedule which required some modification was presented under the acronym "HARDE": Hyperfractionated, Accelerated Radiotherapy *with* Dose Escalation [37]. This regimen prescribed two fractions per day on weekdays with escalating dose per fraction (1.2 Gy week 1 and 2, 1.4 Gy week 3 and 4, 1.6 Gy week 5) and a single dose of 2 Gy on Saturdays to a total dose of 76 Gy in 5 weeks. The intervals between the fractions were at least 6 h. Acute mucosal reactions were described as "extremely brisk". All patients

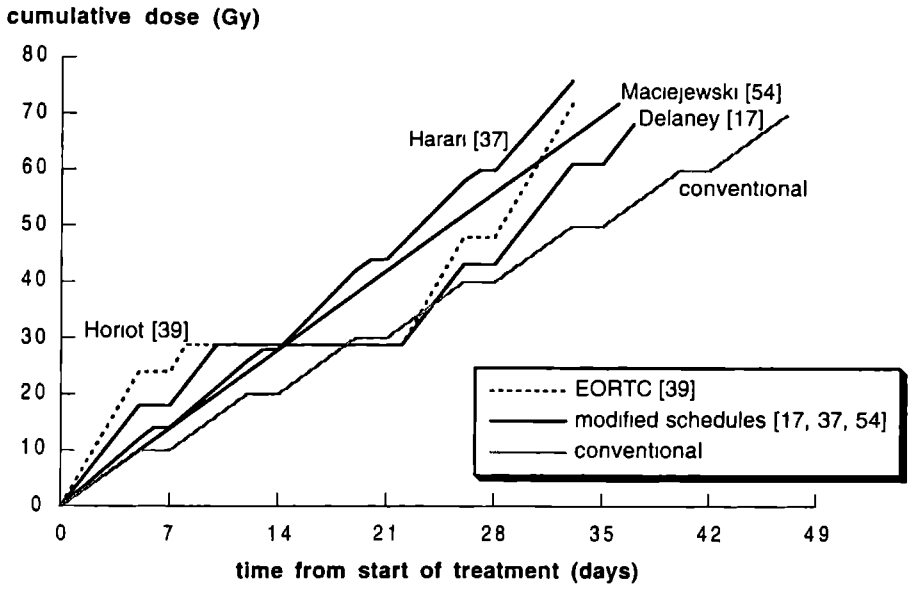


Fig. 4. *Dose accumulation as a function of time for four schedules with moderate reduction of overall treatment time*

developed confluent mucositis Two of 12 patients experienced marked prolongation of acute mucosal toxicity The investigators decided to delete the Saturday fractions, maintaining a dose ≥ 70 Gy over a 5 5 week treatment course

The third regimen producing excessive mucosal toxicity was a split-course schedule [17] Twice daily fractions of 1 8 Gy were administered with intervals of at least 6 h An initial 16 fractions were followed by a 5-12 day break, followed by a further 20-22 fractions to a total dose of 64 8-68 4 Gy over 5-6 weeks Ninety-six percent of patients developed confluent mucositis with a median duration of 7 weeks The actuarial rate of late complications was 47% at 3 years but the investigators were unable to find any relationship between the duration of acute mucositis and the development of late effects It was concluded that the schedule should be modified, mainly to reduce the risk of late complications but also to moderate early mucosal toxicity

From these studies it can be concluded that the tolerance of the upper aerodigestive tract mucosa does not allow acceleration of treatment to less than 5 weeks without a reduction of total dose This applies in particular to continuous course schedules, which is best

exemplified by the study of Maciejewski et al using optimal interfraction intervals of 24 h [54]

As demonstrated by the mouse studies, a possible gain might be obtained by the introduction of splits in the treatment This is not supported by the split-course schedule discussed above [16] although, admittedly, the main reason for modifying this schedule was the high rate of *late* complications Another split-course schedule was tested in EORTC-study 22851 and compared with conventional radiotherapy [39] In the experimental arm 72 Gy was delivered over 33 days Three daily fractions were given to a dose of 28 8 Gy in 8 days After a 12-14 day rest period a second course of 43 2 Gy was given in 11 days In this experimental arm grade 3-4 mucosal reactions (EORTC/RTOG scale) were observed in 67% of the patients during treatment More importantly, these reactions were still present in 70% of patients 6 weeks *after* treatment Grade 3 late mucosal sequelae (deep mucosal necrosis or major mucosal edema requiring tracheostomy) occurred in 13% of the patients in the accelerated arm compared to 5% in the control arm Also, they occurred significantly more rapidly in the accelerated arm The investigators did not find evidence for a consequential effect in their material although the prolonged duration of mucositis and the more rapid occurrence of late sequelae do suggest such a mechanism It was concluded that the boundaries of acceptable acute and late tolerance were reached and recommended that the schedule should be modified to reduce late toxicity It was felt that "acute toxicity did not represent a major obstacle to the feasibility of accelerated schemes"

The EORTC-schedule delivered the same total dose as in Maciejewski's study in a slightly shorter overall time Dose specification was the same The first one was found to approach the limits of acute tolerance but still acceptable whereas the latter clearly exceeded mucosal tolerance with severe consequential damage Distribution by T-stage was more or less the same in both studies but the EORTC-study included more advanced nodal disease Therefore, any differences in treatment volume would probably be disadvantageous for the EORTC-study Maciejewski's study included more larynx and hypopharynx tumors As demonstrated before, the radiation tolerance of the mucosa at these sites is better than in the oropharynx, at least with conventional treatment It is therefore unlikely that the differences in tolerance between these two studies are due to differences in treatment volume or tumor site In the EORTC-study the interval between fractions was only 4 h which may not be optimal according to Bentzen's review [8] Thus, if there is truly a difference in acute tolerance, the explanation should come from the split-course design of the EORTC-study This, on the other hand, is not confirmed by the other split-course schedule discussed above It is also possible that we are confronted with a different subjective interpretation of toxicity data by different investigators

B) Accelerated fractionation with overall treatment time < 33 days but > 17 days, usually with moderate reduction of total dose Two schedules in this group were judged to be unacceptable with respect to acute toxicity, one split-course and one continuous schedule The first one delivered eight fractions of 0 9 Gy per day with 2 h intervals over 5 days [60] After a rest period of 2 weeks an identical series was given to a total dose of 72 Gy over 4 weeks Confluent mucositis occurred in 45% of patients and confluent mucositis *with* ulceration in another 26% In 23% of all patients severe necroses were noted within the first 6 months after treatment Apart from the high dose given in a very short time, the interfraction intervals were most probably too short to allow for sufficient repair of sublethal damage in this schedule The second schedule is another example of pure acceleration [43] The total dose (66 Gy) and dose per fraction (2 Gy) were unchanged relative to conventional treatment and the overall time was reduced to 22-25 days by delivering two fractions per day with an interval of at least 6 h Detailed data on mucositis were not given in this paper but it was stated that most patients developed confluent mucositis and that many of these reactions persisted for weeks and in some cases for months It was also stated that "the clinical outcome in these patients was not unlike that resulting from supralethal dose described half a century ago" It was the excessively prolonged acute reactions in some patients and the high incidence of grade 4 (RTOG scale) late effects (8/41 patients) that caused the Head and Neck tumour group in British Columbia to discontinue the use of this particular accelerated regime

Fig 5 shows these two schedules and some other schedules [10, 11, 16, 19] in this group which were considered as tolerable The two schedules with the higher total dose are the ones exceeding mucosal tolerance confirming the conclusion that reduction of treatment time to less than 5 weeks also requires reduction of the total dose Apparently this reduction must be in the order of 15% Doses of around 60 Gy in 3-4 weeks are within the limits of tolerance It should also be noted that the window is narrow differences in time or dose of only a few days or a few Grays can tilt the balance

Two schedules in this group delivered doses of about 70 Gy in slightly less than 5 weeks and were judged as acceptable [5, 77] One, relatively small study, included patients with oral cavity and oropharynx tumors giving 70 3 Gy over 32 days [5] The investigators judged the mucosal reactions as acceptable However, at 4 months after radiotherapy still 20% of the patients had "major symptoms" related to mucositis which indicates that this schedule is at the margin of tolerance The other study included only patients with nasopharynx tumors and the total dose of 71 4 Gy, given over 30 days, was limited to the primary tumor site [77] Mucositis in the nasopharynx is probably better tolerated because

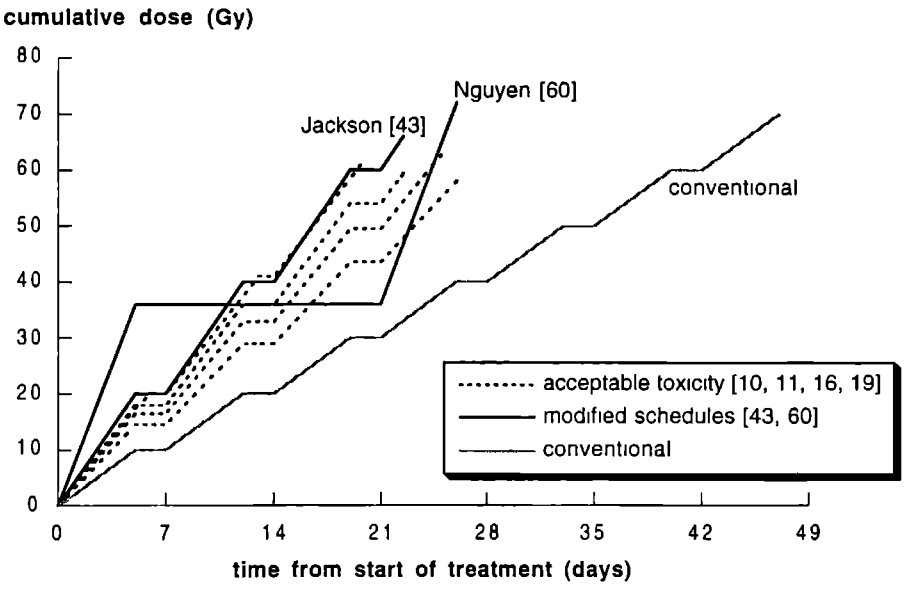


Fig. 5. *Dose accumulation as a function of time for six schedules with overall treatment time < 33 days but > 17 days.*

there is no food passage and possibly also because this mucosa is of a different histological type.

C) Accelerated fractionation with overall treatment time ≤ 17 days and reduction of total dose This type of very accelerated schedules has already been tested in the seventies and early eighties but has only later been taken into large scale clinical studies [20] To deliver a significant dose in a time as short as 2 weeks requires administration of at least three fractions per day To accomplish this goal during normal working hours the interval between fractions can not be more than 4 h. This, in fact, was the case with all the earlier studies where intervals of 3-4 h were used One of the earliest reports on such a schedule was by Svoboda [74] He treated various tumor types like breast, bronchus, bladder and also larynx and hypopharynx carcinomas. Dose per fraction varied from 1.6 to 2 3 Gy but was usually in the order of 1.7-1 8 Gy for the patients with head and neck tumors [75] Total dose varied between 50 and 55 Gy with treatment times of 10-14 days. There were no treatments during weekends. Results in 59 evaluable patients were described The

investigator mentioned that "A mucositis with fibrinous pseudomembranes was observed 3-4 weeks after the start of treatment and the reactions had healed by the end of the second month" Of 19 patients in whom the oral cavity was treated, two had delayed mucosal healing and two others had persistent superficial ulceration of the tongue It was concluded that the early reactions were moderate and well tolerated This approach was adopted by others [35, 52, 63, 67] but conclusions about tolerance differed markedly Peracchia et al treated 22 patients with doses of 48-56 Gy, 2 Gy per fraction, over 8-12 days [67] They describe a confluent mucositis that developed after 2-3 weeks which decreased only very slowly within 4-5 months and led to necrosis in 15 (68%!) patients Nine patients even died because of this complication without evidence of local tumor recurrence The slow healing of the mucosa followed by necrosis (already after 4-8 months in 12 patients) strongly suggests that the latter is a consequential effect As a possible explanation for this disastrous outcome it was suggested by the investigators that repair of sublethal damage in the oropharyngeal mucosa may not be complete 4 h after a dose of 2 Gy A slightly lower dose per fraction of 1 8 Gy was reported to produce acceptable mucosal toxicity in a small study of nine patients [35] Exactly the same schedule caused "unacceptably severe acute reactions" according to other investigators [50] This latter statement was, however, not accompanied by any data The largest published experience with this schedule is by Olmi et al [63] They treated 161 patients with tumors of the oral cavity, oropharynx, and paranasal sinuses Of these, 124 received a total dose of 48-52 Gy, 2 Gy per fraction, over 11-12 days Peak mucosal reactions occurred on average 2 weeks after the start of treatment with complete recovery after 6-10 weeks in most cases There were five patients with transient mucosal ulceration healing within 6 months No relationship was found between acute and late sequelae The interval between fractions in this study was also 4 h The acute reactions were classified as "brisk but still tolerable" Lower doses per fraction of 1 5-1 8 Gy but also with short intervals (3-4 h) were used in a more recent study [52] A total dose of 47 5-54 Gy was delivered over 12-20 days Severe confluent mucositis was reported in 18/58 patients (31%) with denudation of the mucosa in some Modifications including further reduction of total dose and dose per fraction and field shrinking were recommended

Dische et al recently published the results of a randomized multicenter trial of CHART versus conventional radiotherapy in head and neck cancer [20] CHART (continuous, hyperfractionated, accelerated radiotherapy) delivered fractions of 1 5 Gy three times per day including Saturday and Sunday to a total dose of 54 Gy in 36 fractions over 12 days The intervals between the fractions were at least 6 h Five-hundred fifty-two patients were randomized to the experimental arm and 366 to the conventional arm The morbidity related to these schedules was well documented Confluent mucositis occurred in 73% of the

CHART cases compared with 43% in the conventional arm (66 Gy in 33 fractions over 6.5 weeks). Persistence of mucositis for ≥ 6 weeks occurred in 30% of the patients and ≥ 8 weeks in 2% with CHART. In fact, reactions in the CHART cases tended to settle sooner than in the patients treated conventionally. The incidence of late superficial or deep mucosal ulceration was significantly lower with CHART. This regimen proved to be acceptable with regard to acute reactions and was so far associated with a reduced severity in a number of late morbidities compared to conventional treatment.

The acute toxicity of the CHART schedule, although enhanced, is clearly within acceptable limits. When a higher dose per fraction (1.8-2.0 Gy) and shorter interfraction intervals (3-4 h) are used, investigators seem to disagree about tolerance. Apparently with these very accelerated schedules only small variations in treatment time, dose, dose per fraction, and possibly also interfraction intervals can shift enhanced but still acceptable mucosal morbidity towards very severe and intolerable toxicity.

D) Hyperfractionation. Lowering the dose per fraction to 1.1-1.2 Gy and delivering two fractions per day enables dose escalation to about 80 Gy [15, 40]. For oropharynx tumors EORTC study 22791 compared 80.5 Gy given in twice daily fractions of 1.15 Gy over 7 weeks with a conventional treatment to 70 Gy [40]. Objective mucosal reactions were more severe in the experimental arm (67% of patients with confluent mucositis) but tolerable. The incidence of late effects was the same in both arms and in particular there was no increase of late mucosal sequelae with hyperfractionation. This study was preceded by a pilot investigation which tested fraction doses of 1.15 to 1.25 Gy [41]. The lowest dose per fraction allowed the total dose of 80.5 Gy to be given with more tolerable acute mucosal reactions whereas 1.25 Gy twice daily was clearly too toxic. A similar experience was reported from the MD Anderson Cancer Center using hyperfractionation mostly for larynx and hypopharynx carcinomas [32]. Initially a dose per fraction of 1.2 Gy was used with 4 h intervals to a median total dose of 76.8 Gy. Later the protocol was amended to try to decrease a high rate of acute reactions and to maximize the tolerance of late reacting tissues. The interfraction interval was increased to 6 h and for patients receiving wide field nodal irradiation the dose per fraction for the initial fields was reduced to 1.1 Gy. The planned total dose was not changed which implies a treatment protraction of 2 days. A significant reduction of mucositis was observed after these amendments. The incidence of confluent mucositis was reduced from 52 to 37%. Only 4% of the patients had persistent mucositis (i.e. mucositis of 6 weeks duration or greater) versus 14% of the patients treated in the earlier period. To what extent the increase of the interfraction interval and the reduction of fraction dose with consequent increase of overall time have contributed to the increased

tolerance cannot be differentiated Because, with the lower fraction dose, a trend towards worse local control for T_3 tumors was observed, the 1 2 Gy per fraction throughout has been reinstated for this subgroup Apparently, although maybe approaching the limits of tolerance, this schedule is tolerable This is confirmed by the publications from the University of Florida group who also have a large experience with this schedule [66] and by RTOG-study 83-13 [15] The latter study involved a dose escalation in four steps 67 2 Gy, 72 0 Gy, 76 8 Gy, and finally 81 6 Gy Interestingly, in this study no dose-response relationship could be demonstrated for grade 3-4 (RTOG-scale) acute reactions It may well be that the treatment protraction which accompanied this dose escalation was sufficient to allow for complete compensation by mucosal repopulation With each step 2 extra treatment days with two 1 2 Gy fractions were added Bentzen et al calculated an average protraction of 2 8 days (averaging out extra weekends included to finish therapy) for each increase of 4 8 Gy [8] This, according to their calculations, is equivalent to 4 48 Gy in 2 Gy fractions which then corresponds with 1 6 Gy/day This is in agreement with the estimation of daily recovery equivalent to 1 8 Gy/day based on data from Fletcher which was discussed earlier [29, 78]

With this type of hyperfractionated schedules small differences in the daily dose rate of 0 2 Gy can cause observable differences in mucosal reactions, this being particular relevant during the first part of the treatment At the end of the treatment the mucosa is able to almost fully recover the daily dose An escalation of the rate of daily dose delivery might thus improve tolerance, for example using 1 1 Gy fractions during the first part of the treatment and 1 3-1 4 Gy fractions at the end This principle was explored by Harari et al who escalated the fraction dose from 1 2 Gy in the first weeks to 1 6 Gy in the last week of treatment [37] In fact the same is done with concomitant boost type schedules [13, 36, 47, 55]

In summary 1) With continuous course schedules acceleration to treatment times less than 5 weeks requires reduction of the total dose to below 70 Gy Doses of around 60 Gy in 3-4 weeks are within the limits of tolerance It may be advantageous to escalate the rate of dose delivery during treatment and deliver higher daily doses towards the end when the mucosa is most actively repopulating 2) If mucosal tolerance can be improved by introducing a split, the gain is probably small, at least with clinically relevant temporal dose distributions Split-course schedules and also the very short continuous schedules often require that three fractions per day are delivered Intervals between fractions should be sufficiently long, i e $\geq$ 6 h, at least for late reacting tissues but possibly also for mucosa to allow for repair of sublethal damage to approach completion This means that such

treatments can only be delivered if the treatment facility is operational beyond normal working hours 3) Escalating dose by adding treatment days to a 6-7 weeks schedule of hyperfractionation does not seem to significantly enhance mucosal reactions 4) And finally, once approaching the limits of tolerance small variations in treatment time, dose, dose per fraction, and possibly also interfraction intervals can shift enhanced but still acceptable mucosal morbidity towards very severe and intolerable toxicity

Altered fractionation: does the upper aerodigestive tract mucosa limit treatment intensification?

The rate of dose delivery is the most important determinant for early radiation reactions It seems fair to conclude that, relative to a conventional treatment of 7 weeks, the maximum achievable gain in treatment time is 2 weeks with the mucosa being the limiting tissue Any further acceleration requires a reduction of dose Manipulations with the temporal distribution of dose, fraction dose, and optimization of interfraction intervals can improve tolerance but we foresee no possibilities for a significant further intensification of the existing accelerated schedules by such measures

Dose escalation by hyperfractionation however does not seem to be directly limited by early mucosal reactions Late reacting tissues are more likely to limit further intensification of these schedules

Important to remember is that tumors retain many characteristics of the normal tissue from which they originate It is therefore not surprising that the differential between the fractionation sensitivity of squamous cell carcinomas and mucosa is small Some hints for this relationship were found after a retrospective analysis of 286 patients which demonstrated a nonsignificant trend towards higher local tumor failure rates in patients who had lower scores of acute mucositis [32] A similar analysis of data from EORTC trial 22791 which compared hyperfractionation and conventional fractionation for oropharynx carcinomas, on the other hand did not reveal convincing evidence for the existence of such a relationship [9]

Future directions

Randomized studies have proven the effectiveness of altered fractionation for head and neck tumors Improvements of the loco-regional control rate are in the range of 5-23% [2,

16, 20, 39, 40, 65]. As we have reached the limits of tolerance, how must we proceed to further improve treatment outcome? Different strategies can be explored: 1) Application of a potent agent which can prevent or diminish radiation mucositis might permit further intensification of radiotherapy for head and neck carcinomas. 2) Combination of altered fractionation with modifiers of other resistance mechanisms, e.g. hypoxic sensitizers. 3) Individual tailoring of the treatment schedule according to patient and tumor characteristics.

Besides for eventual treatment intensification, any agent that can ameliorate radiation-induced mucositis is of value for diminishing discomfort to the patient. Unfortunately, drugs with sufficient potency have yet to be identified. Sucralfate, an aluminum hydroxide complex of sulfated sucrose introduced for the treatment of gastric ulcers was found to alleviate bowel discomfort during and after pelvic irradiation [38]. The effectiveness of this agent in the head and neck area was tested in six randomized studies but only one showed a positive result [7, 28, 30, 51, 56, 59]. Spijkervet suggested that gram-negative bacteria and possibly also yeasts colonizing the oral tissues may be involved in the pathogenesis of radiation induced mucositis [71]. Elimination of these microorganisms from the oral cavity and oropharynx might then reduce mucositis. In a randomized study which accrued 221 evaluable patients, lozenges containing polymyxin E, tobramycin and amphotericin were compared with placebo [76]. A small subset of patients (14%) was treated with the CHART schedule whilst the others were treated conventionally. Slightly over 60% of patients in both groups developed spotted mucositis. The incidence of confluent mucositis was lower in the experimental arm (14% vs. 27%). The relative mucosal surface affected by spotted or confluent mucositis was 30% versus 40% in the control arm (median values). Although these differences were statistically significant, this antimicrobial prophylaxis is probably not effective enough to allow intensification of fractionation schedules. Unfortunately no details were given on the CHART patients in this study. Also patients with tumors at various sites were included, half of them having larynx or hypopharynx carcinomas. It is not clear whether at these sites adequate concentrations of the drugs are obtained by this particular mode of topical administration and whether the same microorganisms are involved at the different sites. Benzydamine hydrochloride is a nonsteroidal drug that possesses analgetic, anti-inflammatory and antimicrobial properties. In a small randomized study including a total of 43 patients benzydamine as a prophylactic rinse was shown to reduce the area involved by mucositis [27]. However, within this small patient group there was considerable heterogeneity with regard to both tumor localization and dose delivered and the results must be interpreted with some caution. Other potentially useful agents include silver-nitrate, prostaglandins, granulocyte-macrophage colony stimulating factor (GM-CSF), and

immunoglobulins but these have not yet been tested in randomized studies. So far, none of these measures seem compelling enough to be recommended as standard practice.

Accelerated radiotherapy aims to counteract tumor cell repopulation whereas hyperfractionation schedules were designed to overcome intrinsic radioresistance. The third important resistance mechanism is hypoxia. A next step to create a greater differential between normal tissue effects and tumor response is to combine altered fractionation with modifiers of oxygenation. The series of consecutive Danish Head and Neck Cancer Studies (DAHANCA) nicely demonstrates how consequent and stepwise incorporation of radiobiological principles in clinical trials has lead to improved tumor control. In the randomized DAHANCA-5 study it was shown that radiotherapy with the hypoxic sensitizer nimorazole improved loco-regional control in supraglottic and pharyngeal carcinomas from 33 to 49% (5-year actuarial rate) [64]. In the most recent DAHANCA-7 trial reduction of treatment time from 6.5 to 5.5 weeks plus nimorazole gave an additional improvement from 44 to 58% (3-year actuarial rate) [65]. Two mechanisms underlying tumor hypoxia are recognized. Chronic hypoxia results from the limited diffusion distance of oxygen in tissue [79], whereas acute or transient hypoxia is caused by local fluctuations in tumor blood perfusion [12]. "ARCON" combines accelerated radiotherapy with carbogen to reduce chronic tumor hypoxia and with nicotinamide to reduce acute hypoxia. Testing of this strategy in the clinic has recently started and preliminary results are very encouraging. In a phase II study of 62 patients with stage III-IV laryngeal carcinomas an actuarial 2-year local control rate of 92% was obtained [45].

The third strategy involves tools to identify which individual tumors or classes of tumors are most effectively treated by either of the new radiotherapy approaches. However, predictive assays with sufficient discriminating power are not yet available. It is also becoming clear that mechanisms determining the radiation response of tumors are not acting independently and it is very likely that often a combination of factors is responsible for treatment failure. Considering the complexity of the mechanisms involved and the heterogeneity within tumors, it is unlikely that radiation response can be predicted with sufficient accuracy by the value of a single parameter. We must therefore develop assays for simultaneous analysis of multiple resistance factors, if possible, supplemented by assays of normal tissue sensitivity to obtain a "predictive profile". It is not realistic to expect that in the near future all individual patients can be subjected to such extensive testing. The approach may however lead to the identification of *categories* of tumors that are best treated by certain new strategies.

References

1. Ang, K.K., Landuyt, W., Xu, F.-X., Vanuytsel, L. and van der Schueren, E. The effect of small radiation doses per fraction on mouse lip mucosa assessed using the concept of partial tolerance. Radiother. Oncol. 8: 79-86, 1987.

2. Ang, K.K., Trotti, A., Garden, A.S. et al. Overall time factor in postoperative radiation: results of a prospective randomized trial. Radiother. Oncol. 40 (Suppl 1): S30, 1996.

3. Ang, K.K., Xu, F.-X., Landuyt, W., and van der Schueren, E. The kinetics and capacity of repair of sublethal damage in mouse lip mucosa during fractionated irradiations. Int. J. Radiat. Biol. Oncol. Phys. 11: 1977-1983, 1985.

4. Ang, K.K., Xu, F.-X., Vanuytsel, L. and van der Schueren, E. Repopulation kinetics in irradiated mouse lip mucosa: the relative importance of treatment protraction and time distribution of irradiations. Rad. Res. 101: 162-169, 1985.

5. Antognoni, P., Bignardi, M., Cazzaniga, L.F. et al. Accelerated radiation therapy for locally advanced squamous cell carcinomas of the oral cavity and oropharynx selected according to tumor cell kinetics - a phase II multicenter study. Int. J. Radiat. Biol. Oncol. Phys. 36: 1137-1145, 1996.

6. Bäckström, A., Jakobsson, P.Å., Littbrand, B. and Wersäll, J. Fractionation scheme with low individual doses in irradiation of carcinoma of the mouth. Acta Radiol. Ther. Phys. Biol. 12: 401-406, 1973.

7. Barker, G., Loftus, L., Cuddy, P. and Barker, B. The effects of sucralfate suspension and diphenhydramine syrup plus kaolin-pectin on radiotherapy-induced mucositis. Oral Surg. Oral Med. Oral Pathol. 71: 288-293, 1991.

8. Bentzen, S.M., Ruifrok, A.C.C. and Thames, H.D. Repair capacity and kinetics for human mucosa and epithelial tumors in the head and neck: clinical data on the effect of changing the time interval between multiple fractions per day in radiotherapy. Radiother. Oncol. 38: 89-101, 1996.

9. Bernier, J., Thames, H.D., Smith, C.D. and Horiot, J.-C. Tumor response, mucosal reactions and late effects after conventional and hyperfractionated radiotherapy. Radiother. Oncol. 47: 137-143, 1998.

10. Bourhis, J., Fortin, A., Dupuis, O. et al. Very accelerated radiation therapy: preliminary results in locally unresectable head and neck carcinomas. Int. J. Radiat. Biol. Oncol. Phys. 32: 747-752, 1995.

11. Bradley, P.J. and Morgan, D.A.L. Radiotherapy of advanced laryngeal cancer using three small fractions daily. Otolaryngol. Head Neck Surg. 104: 838-841, 1991.

12. Brown, J.M. Evidence for acute hypoxic cells in mouse tumours and a possible mechanism of reoxygenation. Br. J. Radiol. 52: 650-656, 1979.

13. Bujko, K., Skoczylas, J.Z., Bentzen, S.M. et al. A feasibility study of concomitant boost radiotherapy for patients with cancer of the supraglottic larynx. Acta Oncol. 32: 637-640, 1993.

14. Coutard, H. Roentgen therapy of epitheliomas of the tonsillar region, hypopharynx and larynx from 1920 to 1926. Am. J. Roentgenol. & Rad. Therapy 28: 313-331, 1932.

15. Cox, J.D., Pajak, T.F., Marcial, V.A. et al. ASTRO plenary: interfraction interval is a major determinant of late effects, with hyperfractionated radiation therapy of carcinomas of upper respiratory and digestive tracts: results from Radiation Therapy Oncology Group protocol 8313. Int. J. Radiat. Oncol. Biol. Phys. 20: 1191-1195, 1991.

16. Cummings, B.J., Keane, T.J., O'Sullivan, B. et al. A prospective randomized trial of hyperfractionated versus conventional once daily radiation for advanced squamous cell carcinomas of the larynx and pharynx. Radiother. Oncol. 40 (Suppl 1): S30, 1996.

17. Delaney, G.P., Fisher, R.J., Smee, R.I., Hook, C. and Barton, M.B. Split-course accelerated therapy in head and neck cancer: an analysis of toxicity. Int. J. Radiat. Oncol. Biol. Phys. 32: 763-768, 1995.

18. Denham, J.W., Hamilton, C.S., Simpson, S.A. et al. Acute reaction parameters for human oropharyngeal mucosa. Radiother. Oncol. 35: 129-137, 1995.

19. Denham, J.W., Walker, Q.J., Lamb, D.S. et al. Mucosal regeneration during radiotherapy. Radiother. Oncol. 41: 109-118, 1996.

20. Dische, S., Saunders, M.I., Barrett, A., Harvey, A., Gibson, D. and Parmar, M.K.B. A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother. Oncol. 44: 123-136, 1997.

21. Dixit, S., Dvivedi, M.S., Rawat, M. and Gujral, M.S. Hyperfractionation in advanced head and neck cancer. Indian J. Med. Sci. 45: 176-180, 1991.

22. Dobrowsky, W. Unconventional fractionation with or without mitomycin C in advanced head and neck cancer. Sem. Radiat. Oncol. 2: 45-47, 1992.

23. Dörr, W. Repopulation in mouse oral mucosa: treatment splits. Radiother. Oncol. 33: 139-147, 1994.

24. Dörr, W., Breitner, A. and Kummermehr, J. Capacity and kinetics of SLD repair in mouse tongue epithelium. Radiother. Oncol. 27: 36-45, 1993.

25. Dörr, W. and Kummermehr, J. Accelerated repopulation of mouse tongue epithelium during fractionated irradiations or following single doses. Radiother. Oncol. 17: 249-259, 1990.

26. Dörr, W. and Weber-Frisch, M. Repopulation response of mouse oral mucosa during unconventional radiotherapy protocols. Radiother. Oncol. 37: 230-236, 1995.

27. Epstein, J.B., Stevenson-Moore, P., Jackson, S., Mohamed, J.H. and Spinelli, J.J. Prevention of oral mucositis in radiation therapy: a controlled study with benzydamine hydrochloride rinse. Int. J. Radiat. Oncol. Biol. Phys. 16: 1571-1575, 1989.

28. Epstein, J.B. and Wong, F.L. The efficacy of sucralfate suspension in the prevention of oral mucositis due to radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 28: 693-698, 1994.

29. Fletcher, G.H., MacComb, W.S. and Shalek, R.J. Radiation therapy in the management of cancer of the oral cavity and oropharynx. p. 51. Charles C. Thomas, Springfield, MO, 1962.

30. Franzén, L., Henriksson, R., Littbrand, B. and Zackrisson, B. Effects of sucralfate on mucositis during and following radiotherapy of malignancies in the head and neck region. A double-blind placebo-controlled study. Acta Oncol. 34: 219-223, 1995.

31. Fu, K.K., Clery, M., Ang, K.K., Byhardt, R.W., Maor, M.H. and Beitler, J.J. Randomized phase I/II trial of two variants of accelerated fractionated radiotherapy regimens for advanced head and neck cancer: results of RTOG 88-09. Int. J. Radiat. Oncol. Biol. Phys. 32: 589-597, 1995.

32. Garden, A.S., Morrison, W.H., Ang, K.K. and Peters, L.J. Hyperfractionated radiation in the treatment of squamous cell carcinomas of the head and neck: a

comparison of two fractionation schedules. Int. J. Radiat. Oncol. Biol. Phys. 31: 493-502, 1995.

33. Geara, F.B., Peters, L.J., Ang, K.K. et al. Comparison between normal tissue reactions and local tumor control in head and neck cancer patients treated by definitive radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 35: 455-462, 1996.

34. Giri, P.G.S. and Gemer, L.S. Accelerated fractionation radiation therapy for advanced squamous cell carcinoma of the head and neck. South. Med. J. 84: 1103-1107, 1991.

35. Gonzalez Gonzalez, D., Breur, K. and van der Schueren, E. Preliminary results in advanced head and neck cancer with radiotherapy by multiple fractions a day. Clin. Radiol. 31: 417-421, 1980.

36. Gwozdz, J.T., Morrison, W.H., Garden, A.S., Weber, R.S., Peters, L.J. and Ang, K.K. Concomitant boost radiotherapy for squamous carcinoma of the tonsillar fossa. Int. J. Radiat. Oncol. Biol. Phys. 39: 127-135, 1997.

37. Harari, P.M. Adding dose escalation to accelerated hyperfractionation for head and neck cancer: 76 Gy in 5 weeks. Sem. Radiat. Oncol. 2: 58-61, 1992.

38. Henriksson, R., Franzén, L. and Littbrand, B. Effects of sucralfate on acute and late bowel discomfort following radiotherapy of pelvic cancer. J. Clin. Oncol. 10: 969-975, 1992.

39. Horiot, J.C., Bontemps, P., van den Bogaert, W. et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother. Oncol. 44: 111-121, 1997.

40. Horiot, J.C., Le Fur, R., N'Guyen, T. et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother. Oncol. 25: 231-241, 1992.

41. Horiot, J.C., Nabid, A., Chaplain, G. et al. Clinical experience with multiple fractions per day (MFD) in the radiotherapy of head and neck carcinoma. J. Eur. Radiother. 3: 79-89, 1982.

42. Huilgol, N.G., Savithri, S. and Metha, A.R. Discontinuous accelerated fractionation in the treatment of advanced head and neck neoplasms - a preliminary report. Acta Oncol. 32: 84, 1993.

43. Jackson, S.M., Weir, L.M., Hay, J.H., Tsang, V.H.Y. and Durham, J.S. A randomised trial of accelerated versus conventional radiotherapy in head and neck cancer. Radiother. Oncol. 43: 39-46, 1997.

44. Johnson, C.R., Schmidt-Ullrich, R.K. and Wazer, D.E. Concomitant boost technique using accelerated superfractionated radiation therapy for advanced squamous cell carcinoma of the head and neck. Cancer 69: 2749-2754, 1992.

45. Kaanders, J.H.A.M., Pop, L.A.M., Marres, H.A.M. et al. Accelerated radiotherapy with carbogen and nicotinamide (ARCON) for laryngeal cancer. Radiother. Oncol. 48: 115-122, 1998.

46. Kaanders, J.H.A.M., Pop, L.A.M., Marres, H.A.M., van der Maazen, R.W.M., van der Kogel, A.J. and van Daal, W.A.J. Radiotherapy with carbogen breathing and nicotinamide in head and neck cancer: feasibility and toxicity. Radiother. Oncol. 37: 190-198, 1995.

47. Kaanders, J.H.A.M., van Daal, W.A.J., Hoogenraad, W.J. and van der Kogel, A.J. Accelerated fractionation radiotherapy for laryngeal cancer, acute and late toxicity. Int. J. Radiat. Oncol. Biol. Phys. 24: 497-503, 1992.

48. Kajanti, M., Blomqvist, C., Lehtonen, H., Kouri, M., Wiklund, T. and Holsti, L.R. Biweekly dose escalation in curative accelerated hyperfractionation for advanced head and neck cancer: a feasibility study. Int. J. Radiat. Oncol. Biol. Phys. 39: 837-840, 1997.

49. Karim, A.B.M.F., Kralendonk, J.H., Njo, K.H., Tierie, A.H. and Hasman, A. Radiation therapy for advanced ($T_3T_4N_0$-N_3M_0) laryngeal carcinoma: the need for a change of strategy: a radiotherapeutic viewpoint. Int. J. Radiat. Oncol. Biol. Phys. 13: 1625-1633, 1987.

50. Lamb, D.S., Spry, N.A., Gray, A.J., Johnson, A.D., Alexander, S.R. and Dally, M.J. Accelerated fractionation radiotherapy for advanced head and neck cancer. Radiother. Oncol. 18: 107-116, 1990.

51. Lievens, Y., Haustermans, K., Van den Weyngaert, D. et al. Does sucralfate reduce the acute side-effects in head and neck cancer treated with radiotherapy? A double-blind randomized trial. Radiother. Oncol. 47: 149-153, 1998.

52. Lindup, R. Multiple fractions in the treatment of head and neck cancer. Clin. Oncol. 4: 280-283, 1992.

53 Lusinchi, A , Lartigau, E , Luboinski, B and Eschwege, F Accelerated radiation therapy in the treatment of very advanced and inoperable head and neck cancers Int J Radiat Oncol Biol Phys 29 149-152, 1994

54 Maciejewski, B , Skladowski, K , Pilecki, B et al Randomized clinical trial on accelerated 7 days per week fractionation in radiotherapy for head and neck cancer Preliminary report on acute toxicity Radiother Oncol 40 137-145, 1996

55 Mak, A C , Morrison, W H , Garden, A S , Ang, K K , Goepfert, H and Peters, L J Base-of-tongue carcinoma treatment results using concomitant boost radiotherapy Int J Radiat Oncol Biol Phys 33 289-296, 1995

56 Makkonen, T A , Bostrom, P , Vilja, P and Joensuu, H Sucralfate mouth washing in the prevention of radiation-induced mucositis a placebo-controlled double-blind randomized study Int J Radiat Oncol Biol Phys 30 177-182, 1994

57 Marcial, V A , Pajak, T F , Chang, C , Tupchong, L and Stetz, J Hyperfractionated photon radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, pharynx, larynx, and sinuses, using radiation therapy as the only planned modality (preliminary report) by the Radiation Therapy Oncology Group (RTOG) Int J Radiat Oncol Biol Phys 13 41-47, 1987

58 Medini, E , Rao, Y , Kim, T and Levitt, S H Radiation therapy for advanced head and neck squamous cell carcinoma using twice-a-day fractionation Am J Clin Oncol 8 65-68, 1985

59 Meredith, R , Salter, M , Kim, R et al Sucralfate for radiation mucositis results of a double-blind randomized trial Int J Radiat Oncol Biol Phys 37 275-279, 1997

60 Nguyen, T D , Panis, X , Legros, M and Froissart, D Hyperfractionated radiotherapy in advanced squamous cell carcinoma of the head and neck Int J Radiat Oncol Biol Phys 9 393-395, 1983

61 Nissenbaum, M , Browde, S , Bezwoda, W R , de Moor, N G and Derman, D P Treatment of advanced head and neck cancer multiple daily dose fractionated radiation therapy and sequential multimodal treatment approach Med Pediatr Oncol 12 204-208, 1984

62 Notter, G and Turesson, I Clinical randomized pilot studies on multiple fractions a day In Proceedings of Varian's Fourth European Clinac Users Meeting, Malta, May 25-26, 1984, pp 64-69 Varian, Switzerland, 1984

63. Olmi, P., Cellai, E., Chiavacci, A. and Fallai, C. Accelerated fractionation in advanced head and neck cancer: results and analysis of late sequelae. Radiother. Oncol. 17: 199-207, 1990.

64. Overgaard, J., Sand Hansen, H., Overgaard, M. et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) protocol 5-85. Radiother. Oncol. 46: 135-146, 1998.

65. Overgaard, J., Sand Hansen, H., Overgaard, M. et al. Conventional radiotherapy as primary treatment of squamous cell carcinoma of the head and neck. A randomized multicenter study of 5 versus 6 fractions per week - report from the DAHANCA 7 trial. Int. J. Radiat. Oncol. Biol. Phys. 39 (Suppl): 188, 1997.

66. Parsons, J.T., Mendenhall, W.M., Stringer, S.P., Cassisi, N.J. and Million, R.R. Twice-a-day radiotherapy for squamous cell carcinoma of the head and neck: the University of Florida experience. Head Neck 15: 87-96, 1993.

67. Peracchia, G., Salti, C. Radiotherapy with thrice-a-day fractionation in a short overall time: Clinical experiences. Int. J. Radiat. Oncol. Biol. Phys. 7: 99-104, 1981.

68. Pinto, L.H.J., Canary, P.C.V., Araújo, C.M.M., Bacelar, S.C. and Souhami, L. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 21: 557-562, 1991.

69. Sanchíz, F., Millá, A., Torner, J. et al. Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. Int. J. Radiat. Oncol. Biol. Phys. 19: 1347-1350, 1990.

70. Schwade, J.G., Markoe, A.M., Abitbol, A.A. et al. Accelerating hyperfractionation for carcinoma of the head and neck. Sem. Radiat. Oncol. 2: 51-53, 1992.

71. Spijkervet, F.K.L. Irradiation mucositis and oral flora. Reduction of mucositis by selective elimination of oral flora. Thesis, University of Groningen, 1989.

72. Stüben, G., Landuyt, W., van der Schueren, E., van der Kogel, A.J. and Reijnders, A. Estimation of repair parameters in mouse lip mucosa during continuous and fractionated low dose-rate irradiation. Radiother. Oncol. 20: 38-45, 1991.

73. Stuben, G., van der Kogel, A J and van der Schueren, E. Biological equivalence of low dose rate to multifractionated high dose rate irradiations: investigations in mouse lip mucosa. Radiother. Oncol 42· 189-196, 1997

74. Svoboda, V H.J. Radiotherapy by several sessions a day. Br. J. Radiol 48: 131-133, 1975.

75. Svoboda, V.H J. Accelerated fractionation. The Portsmouth experience 1972-1984 In: Proceedings of Varian's Fourth European Clinac Users Meeting, Malta, May 25-26, 1984, pp. 70-75. Varian, Switzerland, 1984

76. Symonds, R.P , McIlroy, P., Khorrami, J. et al. The reduction of radiation mucositis by selective decontamination antibiotic pastilles: a placebo-controlled double-blind trial. Br. J Cancer 74: 312-317, 1996.

77. Teo, P.M.L., Kwan, W.H., Leung, S F et al. Early tumour response and treatment toxicity after hyperfractionated radiotherapy in nasopharyngeal carcinoma. Br J. Radiol. 69: 241-248, 1996.

78. Thames, H D., Bentzen, S M , Turesson, I , Overgaard, M. and van den Bogaert, W Time-dose factors in radiotherapy: a review of the human data. Radiother. Oncol 19. 219-235, 1990.

79 Thomlinson, R H. and Gray, L H. The histological structure of some human lung cancers and the possible implications for radiotherapy Br. J Cancer 9: 539-549, 1955.

80. Van den Bogaert, W., van der Schueren, E., Horiot, J C et al The feasibility of high-dose multiple daily fractionation and its combination with anoxic cell sensitizers in the treatment of head and neck cancer Int J Radiat. Oncol. Biol Phys 8. 1649-1655, 1982

81. Van der Schueren, E., van den Bogaert, W., Vanuytsel, L and van Limbergen, E. Radiotherapy by multiple fractions per day (MFD) in head and neck cancer: acute reactions of skin and mucosa. Int. J. Radiat. Oncol Biol. Phys. 19. 301-311, 1990.

82 Wang, C.C., Blitzer, P H. and Suit, H.D Twice-a-day radiation therapy for cancer of the head and neck Cancer 55· 2100-2104, 1985.

83. Zackrisson, B., Franzén, L., Henriksson, R. and Littbrand, B. Tolerance to accelerated fractionation in the head and neck region. Acta Oncol. 33. 391-396, 1994

CHAPTER 4

A CONVENIENT AND RELIABLE METHOD FOR CARBOGEN BREATHING IN MAN

Johannes H.A.M. Kaanders

Richard W.M. van der Maazen

Reprinted from: Radiother. Oncol. 29: 341-343, 1993

with permission from Elsevier Science

Abstract

The feasibility of carbogen breathing and the intake of nicotinamide in combination with radiation therapy is currently being tested for clinical application A dependable and convenient system for carbogen breathing is presented which can be easily combined with techniques for immobilization of the patient The proposed method ensures adequate breathing of carbogen

Introduction

Recent experimental studies have led to a renewed interest in the clinical use of agents to reduce hypoxia in malignant tumors. These studies have shown the effectiveness of both nicotinamide and carbogen breathing on the differential response to radiation of malignant and normal tissues in fractionated X-ray treatments [4]. The results are promising and encourage the clinical use of these two modalities, which are by themselves non-toxic in man, in phase I and II trials. Dische et al. recently presented a pilot study on the effect of carbogen breathing on mainly lung carcinomas and demonstrated a remarkably good local control [2]. Also the EORTC has shown interest in the use of carbogen breathing in combination with the intake of nicotinamide and accelerated fractionation regimens (ARCON) and initiated a phase I-II study for several tumor types [3]. Some centers have already started to study the feasibility of carbogen breathing and the intake of nicotinamide in combination with radiation therapy, and preliminary results were presented in the first ARCON Newsletter [1].

At the Institute of Radiotherapy of the University Hospital Nijmegen, phase I-II studies, which combine carbogen breathing and nicotinamide with radiation therapy, were initiated for patients with stage III and IV head and neck tumors and patients with malignant brain tumors. For this category of patients it was necessary to combine a reliable and convenient way of carbogen breathing with a proper method for immobilization of the patient during irradiations. Breathing through a scuba-diving rubber mouth piece with the nose clipped (to prevent the inspiration of air), as proposed by Dische et al. [2], was tried by patients and healthy volunteers. Although the method is shown to be feasible it was an unpleasant experience, especially for patients with tumors in the upper airway and/or disturbed respiratory reflexes. Clipping the nose obstructs the air passage through the nose and hinders the normal swallowing act, in particular when patients are in a supine position. Furthermore, it is difficult to adjust the constant flow of carbogen (recommended, 10 l/min) to personal needs and it can increase expiratory resistance.

To improve patient comfort during irradiations, we developed a new method of carbogen breathing that can be used in combination with conventional fixation techniques in the head and neck region.

Materials and Methods

Requirements to be met by our system were to enable normal swallowing during carbogen breathing and to regulate carbogen delivery to the individual's needs with minimal resistance from the breathing system In addition, such a breathing system should permit the use of immobilizing casts Normal swallowing is only possible with unobstructed nasal passage Therefore, a disposable anesthetic face mask (Artec Inc Indianapolis, USA) with a silicone cuff, covering both mouth and nose, was selected The silicone cuff is designed in such a way that only slight pressure seals the breathing space airtight These face masks are available in three sizes To transport the gas from the high pressure (30-150 atmos) reservoir to the patient, a scuba-diving breathing regulator (Scubapro, Brussels, Belgium), which consists of two stages, is used The first stage is attached to the reservoir and reduces pressure to approximately 9 atmos An intermediate pressure hose leads the gas to the second stage which further reduces pressure to a breathable level This second stage is connected to the face mask (Fig 1) which is incorporated in the immobilizing cast A two-step pressure reduction is utilized for safety and to allow the use of a "demand valve type" in the second stage This second stage can be tuned in such a way that the slightest demand for air is responded to almost immediately without any extra effort The valves in this system prevent flow of carbogen during exhalation such that no extra expiratory effort is needed

Both Orfit (Ortomed, Schiedam, The Netherlands) and Scotch (3-M, Zoeterwoude, The Netherlands) material, used for fabrication of immobilizing casts, appeared to be appropriate for combining with the anesthetic mask Both materials are heated before use and melt together with the plastic of the anesthetic mask The fixating casts ensure a tight coverage of mouth and nose by the anesthetic mask and offer sufficient pressure to guarantee an airtight breathing space without leakage of air (Fig 2)

Effect of carbogen breathing on arterial O_2 pressure and hemoglobin saturation

The effect of carbogen breathing on arterial O_2 pressure (pO_2) and hemoglobin O_2 saturation was tested in three male healthy volunteers Before and after a 5-min period of carbogen breathing, utilizing the above presented method, blood samples were obtained from the femoral arteries Only a slight increase was observed in the saturation of oxyhemoglobin This was expected since the saturation of hemoglobin by oxygen is already

Fig. 1. *The disposable anesthetic face mask with the special silicone cuff connected to the second stage of the scuba-diving breathing regulator.*

nearly complete in arterial blood of healthy persons. The increase of dissolved oxygen in plasma, however, was significant. Initial pO_2 values were 13.8, 16.0, and 14.0 kPa in the three volunteers and rose to 74.2, 82.5, and 76.6 kPa, respectively, after carbogen breathing. The breathing of carbogen was experienced as rather convenient not only by the volunteers but also by the 25 patients that have entered the studies to date. Only one patient with severe claustrophobia was unable to cope with the procedure.

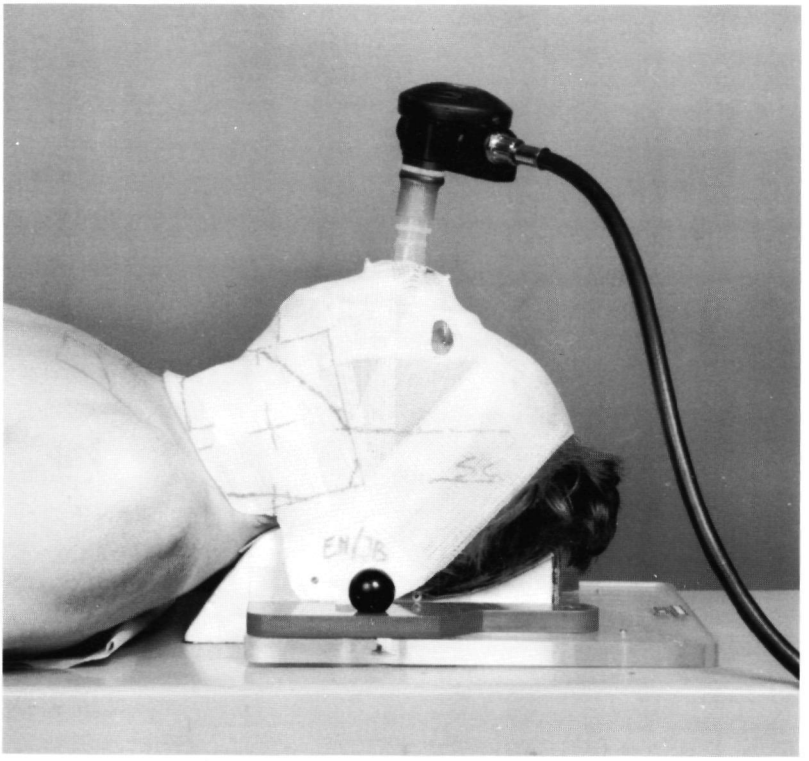


Fig. 2. *Carbogen breathing patient. The anesthetic face mask covers both nose and mouth and is incorporated in an immobilizing cast (Scotch). The mask is connected to the reservoir with carbogen by the scuba-diving breathing regulator.*

Conclusion

Radiation oncologists who participate in the new EORTC ARCON study [3] or in any other clinical study which combines radiation therapy with carbogen breathing, need a reliable and convenient method of administering the gas. A method based on professional diving equipment was designed which can be combined with standard fixation techniques in the head and neck region and minimizes discomfort during treatment. Of the 25 patients who have entered our studies to date, only one was unable to cope with the breathing system, and this was due to extreme claustrophobia. The influence of 5 min carbogen breathing by

the presented method on arterial O_2 pressure was tested in three healthy volunteers. The desired effect, i.e. an increase in arterial O_2 pressure, was easily achieved.

Acknowledgements

The authors wish to thank M.C. Zahradnik, C.J. van der Duin, and S.J. Mulder and associates for excellent collaboration.

References

1. Cancer Research Campaign, ARCON Newsl.1, 1993.

2. Dische, S., Rojas, A., Rugg, T., Hong, A., and Michael, B.D. Carbogen breathing - a system for use in man. Br. J. Radiol. 65: 87-90, 1992.

3. European Organization for Research and Treatment of Cancer. Protocol no. 22923. ARCON: Accelerated Radiotherapy with Carbogen and Nicotinamide. A phase I/II study. Study coordinator: Bernier, J., Department of Radiotherapy, Ospedale San Giovanni, 6500 Bellinzona, Switzerland.

4. Kjellen, E., Joiner, M.C., Collier, J.M., Johns, H., and Rojas, A. A therapeutic benefit from combining normobaric carbogen or oxygen with nicotinamide in fractionated X-ray treatments. Radiother. Oncol. 22: 81-91, 1991.

CHAPTER 5

RADIOTHERAPY WITH CARBOGEN BREATHING AND NICOTINAMIDE IN HEAD AND NECK CANCER: FEASIBILITY AND TOXICITY

Johannes H.A.M. Kaanders

Lucas A.M. Pop

Henri A.M. Marres

Richard W.M. van der Maazen

Albert J. van der Kogel

Willem A.J. van Daal

Reprinted from: Radiother. Oncol. 37: 190-198, 1995

with permission from Elsevier Science

Abstract

The feasibility and early toxicity of radiotherapy with carbogen breathing and nicotinamide was tested in 74 head and neck cancer patients. Forty patients with laryngeal and hypopharyngeal tumors were treated with an accelerated schedule combined with carbogen alone (16) or with carbogen and nicotinamide (24). Thirty-four patients with far advanced unresectable tumors of the oral cavity and oropharynx received conventional radiotherapy with carbogen (16) or with carbogen and nicotinamide (18).

Some enhancement of skin reaction was observed with nicotinamide but this remained well within the limits of tolerance. With the accelerated regimen there was increased severity of mucosal damage expressed as confluent mucositis in 95% of the patients which required healing times of 3-4 months in four patients. Eventually restoration of the mucosal lining was complete in all cases. Nausea and vomiting are the most frequent side-effects of nicotinamide and were reported by 60 and 36% of the subjects, respectively. In 26% this was reason to discontinue drug intake. Severe renal dysfunction was associated with nicotinamide intake in two patients of this study and in one other patient who presented later.

It is our conclusion that radiotherapy combined with carbogen and nicotinamide is a safe treatment with manageable side-effects. We recommend not to give nicotinamide concomitantly with nephrotoxic medication or to patients who have impaired renal function. Preliminary tumor control rates are encouraging and clinical testing will be continued.

Introduction

It is well recognized that hypoxia is an important factor determining the radiation response of squamous cell carcinomas. In man, the existence of hypoxia and its relationship to the outcome of radiation therapy has been demonstrated in carcinomas of the head and neck and uterine cervix [5, 9, 18, 19]. Randomized clinical trials with hyperbaric oxygen and hypoxic cell radiosensitizers have shown significantly improved local control rates in carcinomas of the head and neck [7, 8, 21, 22]. However, these approaches have not gained general acceptance. The side-effects of many radiosensitizers hamper their clinical use although some newer drugs are less toxic. Delivery of radiation in hyperbaric oxygen is a demanding technique and often hypofractionation has been used, but this is currently not considered optimal because of reduced sparing of late reacting normal tissues.

Two mechanisms underlying tumor hypoxia are recognized. Chronic hypoxia results from the limited diffusion distance of oxygen in tissue [27], whereas acute or transient hypoxia is caused by local fluctuations in tumor blood perfusion [2, 3]. Agents that modify tumor microcirculatory function may reduce acute hypoxia. The amide derivative of vitamin B_3, nicotinamide, has recently received attention in this respect [11, 16]. It was suggested that nicotinamide could further enhance the sensitizing effect of carbogen as a method to eliminate chronic hypoxia [24]. Polarographic studies have shown that carbogen (95% O_2 + 5% CO_2) breathing can increase the oxygen partial pressure and reduce chronic hypoxia in patients with head and neck tumors [20]. Relative to radiation treatment in air without the drug, enhancement ratios in the order of 1.8 have been obtained for treatment with carbogen and nicotinamide in mouse tumors [17].

Another important factor determining the radiation response of tumors is cellular repopulation. There is evidence from clinical studies that patients with head and neck carcinomas may benefit from accelerated fractionated irradiation to counteract repopulation of tumor clonogens which occurs during the course of treatment [1, 26]. Results of randomized trials are expected soon.

Rojas et al. proposed the strategy of combining accelerated radiotherapy with carbogen and nicotinamide (ARCON) to overcome both the compensating effect of tumor repopulation and chronic and acute hypoxia [25]. This is a report on the feasibility and toxicity of this approach in patients with carcinomas of the head and neck.

Patients and Methods

Design of the study Two categories of patients were eligible for the study One category includes patients with laryngeal (stage III-IV) and hypopharyngeal (stage II-IV) tumors receiving primary radiotherapy as larynx conserving treatment The other category of patients had far advanced unresectable tumors, mostly of the oral cavity and oropharynx and were referred for palliative radiotherapy It was planned to first treat 15 patients with carbogen alone in each category After this had been shown to be feasible and without severe direct toxicity, nicotinamide was added Since experience was previously obtained with an accelerated schedule in laryngeal cancers [13], it was decided to build on this experience and to add carbogen and nicotinamide as second and third steps, respectively For the oral cavity and oropharyngeal tumors carbogen breathing and nicotinamide were added stepwise to a conventional radiation schedule The patients with laryngeal and hypopharyngeal tumors were analyzed separately from those with oral cavity and oropharyngeal tumors because normal tissue effects as well as treatment outcome are expected to be different in the two groups

This work was approved by the local ethical committee

Patients Seventy-four consecutive patients were entered into the study over the period November 1992 until February 1995 Inclusion criteria were an age over 18 years, WHO performance status of 0-2, no severe heart or lung disease, no severe liver or kidney function disturbances, no severe stridor, no distant metastases, and written informed consent Another six patients were eligible but refused participation Thirteen patients were ineligible for the following reasons poor performance status (9), severe cardiac and pulmonary disease (4), claustrophobia (1), and Rendu-Osler-Weber disease with severe anemia (1) The patients entered in the study had a mean age of 57 years (range 27-82 years) There were 60 men and 14 women All patients had squamous cell carcinomas except one with a mucoepidermoid carcinoma of the larynx Three patients had two concurrent primary tumors in the head and neck area Two other patients had recurrent disease after surgical treatment Characteristics of the patients, their tumors, and the treatment are shown in Table 1

Radiotherapy The primary tumor and bilateral neck nodes were irradiated through lateral opposed photon beams (4 and 6 MV) The inferior border was generally placed just superior to the arytenoids for oral cavity and oropharyngeal tumors For tumors of the

Table 1. *Number of patients according to treatment (RT = radiotherapy, conv = conventional, acc = accelerated, carb = carbogen, nic = nicotinamide) and site of primary disease and clinical stage (UICC 1992 staging system).*

	Treatment			
	Conv RT + carb	**Conv RT + carb + nic**	**Acc RT + carb**	**Acc RT + carb + nic**
No. patients	16	18	16	24
Mean age (range)	55 (41-76)	53 (27-73)	60 (39-82)	60 (41-78)
Stage T_x	–	1[b]	–	–
T_1	2	–	–	–
T_2	–	–	7	7
T_3	5[a]	8[c]	8	13
T_4	8	9	1	4
N_0	3	3	6	11
N_1	2	4	7	5
N_{2a}	–	–	–	–
N_{2b}	1	5	2	1
N_{2c}	8	4	1	7
N_3	1	2	–	–
not classable	1	–	–	–
Site of primary				
oral cavity				
oral tongue	1	3	–	–
floor of mouth	–	5[b]	–	–
oropharynx				
soft palate	1	1	–	–
tonsillar fossa	5	5[c]	–	–
base of tongue	7[a]	3	–	–
pharyngeal wall	1	–	–	–
maxillary sinus	–	1	–	–
auditory canal	1	–	–	–
larynx				
supraglottic	–	–	10	11
glottic	–	–	3	5
hypopharynx				
pyriform sinus	–	–	2	6
postcricoid	–	–	1	2
No. patients receiving chemotherapy	8	8	–	2

[a]One patient with synchronous second primary of soft palate (T_2).
[b]One patient with synchronous second primary of pyriform sinus (T_2).
[c]One patient with synchronous second primary of vallecula (T_1).

larynx and hypopharynx the inferior border was placed just above the shoulders. After 30-40 Gy, an off-cord reduction was made and the posterior cervical chains were treated with lateral appositional electron beams. The mid- and lower-neck nodes were treated with an anterior photon field. In some cases a posterior field was added to supplement the dose in the posterior midcervical chains. The boost dose was delivered through reduced lateral or oblique opposed portals combined, when necessary, with an electron beam to boost nodal areas overlying the spinal cord or larynx. Conventional radiotherapy was given in fractions of 2 Gy, five times a week. Total dose was 68 Gy for gross disease and 44 Gy for the areas treated electively. The overall treatment time was 46-48 days. With the accelerated schedule, the dose per fraction remained 2 Gy but treatment time was reduced by 10 days by giving two fractions per day during the last one and a half weeks of treatment. Intervals between fractions were at least 6 h.

Sensitization of the laryngeal cartilage has been reported after radiotherapy in hyperbaric oxygen [8]. A 10% reduction of the total dose in a subsequent study of hyperbaric oxygen reduced the laryngeal complications to a level seen with treatment in air [7]. Since a similar effect might be expected from normobaric carbogen with nicotinamide, the maximal permissible dose to the larynx was reduced from 70 to 64 Gy and, as a consequence, the tumor dose for primaries of the larynx and hypopharynx did not exceed this limit. Involved nodes received 68 Gy. Because a decrease in the tolerance of the rat spinal cord of ~20% was observed when radiation was combined with carbogen and nicotinamide [6], the total dose to the spinal cord was not higher than 40 Gy. Dose specification was according to Report 29 of the ICRU [12].

Carbogen breathing: Scuba-diving equipment was used for carbogen delivery. This system transports the gas from the reservoir to the patient by way of a two-step pressure reduction. The second stage of the breathing regulator is connected to a disposable anesthetic face mask which is incorporated in the immobilizing cast. Details of this breathing system have been described earlier [14]. Carbogen breathing commenced 4 min before start of irradiation of the macroscopic tumor localizations and was continued throughout the treatment. During the 4-min preirradiation breathing time fields were set up and uninvolved supraclavicular nodes were treated. The preirradiation breathing time and total breathing time were recorded.

Nicotinamide: Nicotinamide, dissolved in fruit juice, was administered orally 1.5 h before irradiations. On days when two fractions were given, only one dose of nicotinamide was taken before the first treatment. Initially the daily dose was 6 g. After April 1994, when

more pharmacokinetic data became available, this was changed to a weight-adjusted dose of 80 mg/kg with a maximum of 6 g.

Monitoring during treatment: Blood pressure and heart rate were measured on the first 5 treatment days just before and after irradiations. This was discontinued after the first 20 patients because no changes had been observed.

Blood samples were drawn once a week for blood cell counting and hemoglobin concentration measurement. When hemoglobin concentrations fell below 7 mmol/l this was corrected by blood transfusions. Initially, serum liver enzymes, sodium, potassium, urea, and creatinine were determined before and in the last week of the treatment. Later this was also done weekly during the course of irradiation.

Weekly assessment of the acute mucosal and skin reactions started in the first week of treatment and continued during treatment and thereafter until the lesions started to heal. Patients were then seen once every 2 or 3 weeks until healing was complete. The reactions of mucosa and skin and dysphagia were scored as shown in Table 2. Since 1987 this

Table 2. *Scores for mucosal and skin reactions.*

	Acute reactions	Score
Mucosa	normal	0
	slight redness	1
	severe redness	2
	spotted mucositis	3
	confluent mucositis ≤ 50% of irradiated surface	4
	confluent mucositis > 50% of irradiated surface	5
Dysphagia	no complaints	0
	complaints, no medication	1
	medication needed	2
	liquid feeding	3
	tube feeding	4
Skin	normal	0
	slight redness	1
	severe redness	2
	dry desquamation	3
	moist desquamation ≤ 50% of irradiated surface	4
	moist desquamation > 50% of irradiated surface	5

scoring system is applied routinely to all patients receiving radiotherapy to the head and neck area in our institute.

Additional treatment: Eighteen patients received chemotherapy prior to radiation treatment. In most cases this consisted of cisplatin weekly for one to six courses. One patient was treated with three courses of methotrexate, bleomycin, vinblastine, and cisplatin. All these patients had far advanced unresectable tumors. After radiotherapy two patients underwent neck dissections for residual nodal disease.

Statistics: Fisher's exact probability test was used to test the significance of differences in acute toxicity scores between the groups. Average duration of mucosal and skin reactions was compared by the *t*-test.

Results

Carbogen breathing: The measurements of blood pressure and heart rate before and after carbogen breathing were discontinued after no apparent changes were observed in the first 20 patients. Six of the 74 patients were unable to continue carbogen breathing throughout the entire course of irradiation. Two patients underwent a tracheostomy, one because of edema and the other because of tumor progression; the other four patients experienced sensations of suffocation, sometimes accompanied by extreme hyperventilation. Preirradiation breathing time was less than 4 min in 1.2% (25/2123) of radiation sessions but never less than 3 min. It was longer than 6 min in 5.8%, usually due to delays in the treatment set up. The total breathing time was more than 15 min 6.7% of times, mostly when complicated techniques were used to limit the dose to the spinal cord.

Nicotinamide: The most common side-effects from nicotinamide were nausea and vomiting, reported, respectively, by 25 (60%) and 15 (36%) of the 42 patients taking the drug. Ten patients were nauseous after the first dose of nicotinamide. Often these complaints were unresponsive to anti-emetics including ondansetron. Eleven patients (26%) discontinued the intake of nicotinamide due to severe nausea and vomiting. One patient was under treatment when adjustments of nicotinamide dose were made from 6 g to individual weight-corrected doses. In this patient nausea disappeared when the dose was reduced from 6 g to 4 g (80 mg/kg). Apart from this one patient we observed no differences in side-effects between patients taking 6 g and those taking 80 mg/kg. Five patients reported flushing 0.5-

2 h after ingestion One patient showed signs of depression which disappeared within a few days after nicotinamide was discontinued One patient refused to continue nicotinamide intake because of the bad taste No serum liver enzyme disturbances related to nicotinamide were observed Twelve patients had isolated elevation of γ-glutamyl transpeptidase (γ-GT), mostly already before start of treatment, which was ascribed to alcohol abuse

Two patients developed severe renal dysfunction following nicotinamide administration Patient 1 received daily doses of 6 g and patient 2 received 5 5 g Both patients complained of nausea and vomiting and patient 2 also had severe diarrhea This was reason to discontinue the drug in both patients Both were admitted to the hospital a few days later with dehydration and renal dysfunction Patient 1 was known to suffer from type I diabetes mellitus and hypertension and concomitant medication consisted of insulin, lisinopril (angiotensin converting enzyme -ACE- inhibitor), bisoprolol (selective ß-blocker), carbasalatcalcium and ondansetron Patient 2 was on metoclopramide, oxazepam, and an antacid Prior to the start of radiotherapy he received six weekly cycles of cisplatin, 70 mg/m^2 Maximum recorded serum levels of creatinine were 2290 µmol/l in patient 1 and 1096 µmol/l in patient 2 Renal function recovered with rehydration and bicarbonate administration in both patients In addition, both patients developed thrombopenia of uncertain etiology Patient 1 also had moderate and transient elevation of liver enzymes 2 weeks after discontinuation of nicotinamide She fully recovered and could resume radiotherapy Patient 2 had an episode of ventricular tachycardia, possibly as a result of electrolyte disturbances He had a large unresectable tumor and progression of disease already under chemotherapy and it was decided to stop further radiation treatment because of the very poor prognosis

Radiotherapy Three patients did not complete the planned radiation treatment One patient died from a massive bleeding in the tumor, one patient developed distant metastases during loco-regional treatment and the third patient as mentioned above had rapid tumor progression, renal complications and deterioration of general condition Total treatment duration exceeded 48 days in four of the 34 patients treated according to the conventional schedule Reasons were renal complications (6 days), tracheostomy (1 day), machine breakdown (1 day), holiday, not compensated for (1 day) Of the 40 patients treated by the accelerated schedule only one surpassed the maximum allowed treatment time of 38 days with a single day because of a holiday that was not compensated for

Early reactions of mucosa and skin The scores for acute radiation reactions during and after treatment are shown in Figs 1 and 2 Only the highest scores are shown because

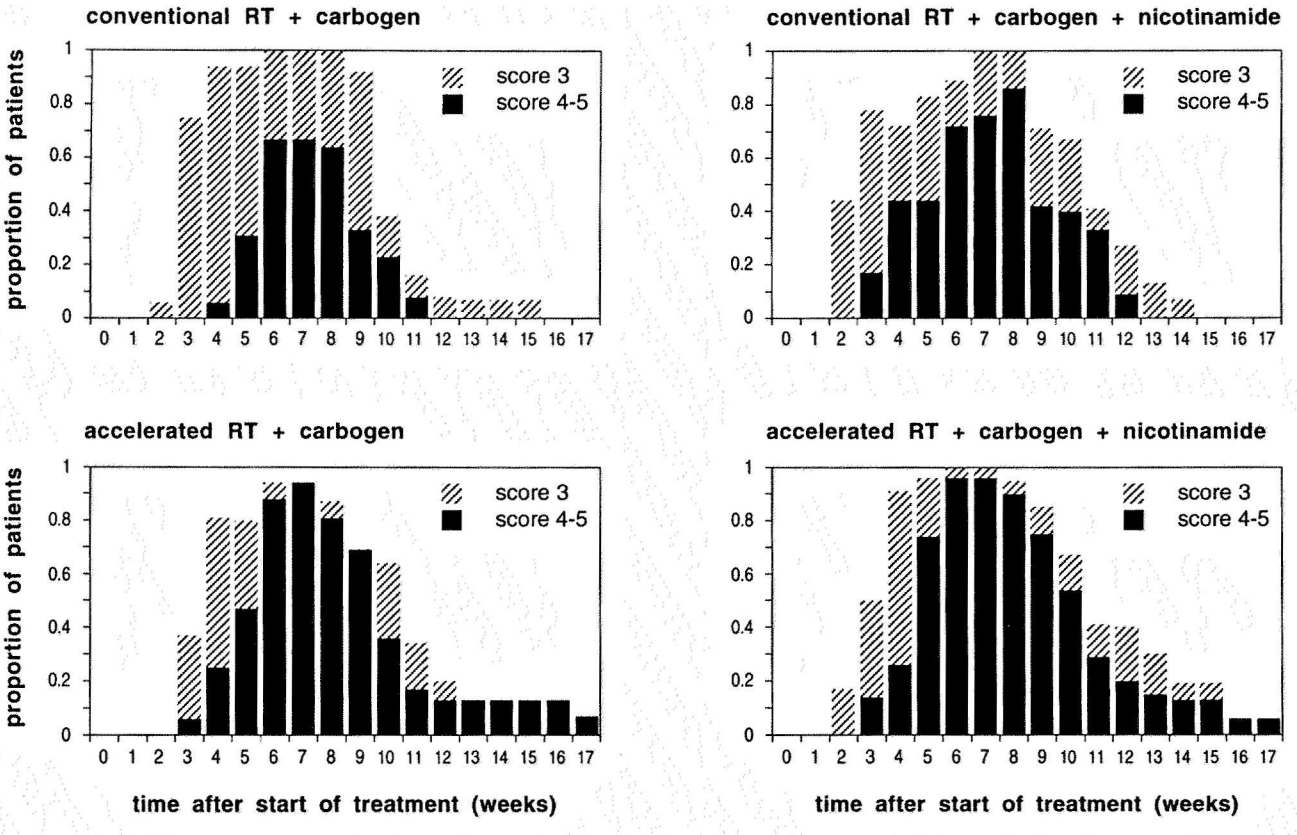


Fig. 1. *Scores for mucosal reactions: proportion of patients reaching a certain score versus time after start of radiotherapy (RT).*

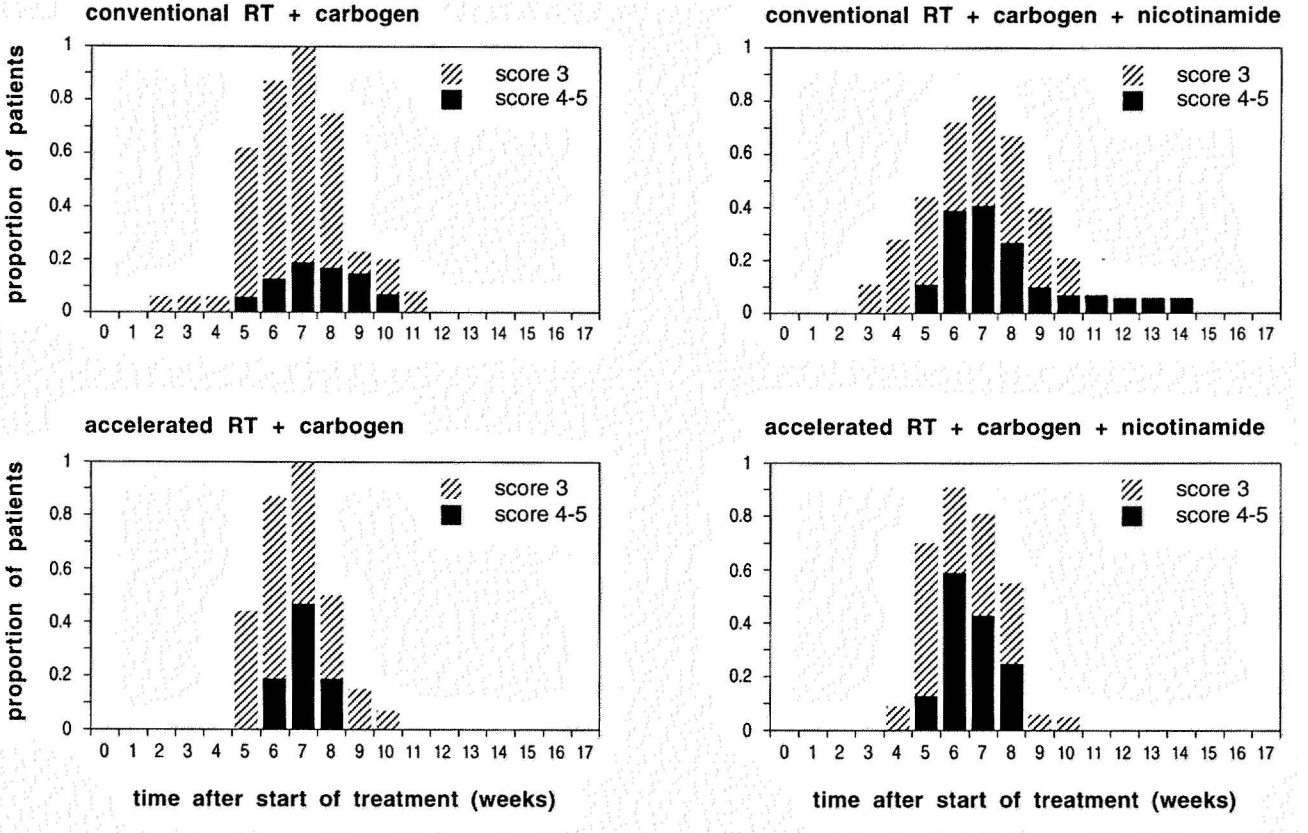


Fig. 2. *Scores for skin reactions: proportion of patients reaching a certain score versus time after start of radiotherapy (RT).*

scores 1 and 2 have limited clinical significance and are nearly always followed by more severe reactions For the group of patients treated with conventional radiotherapy and carbogen (C) confluent mucositis occurred in 81% of the cases, and with addition of nicotinamide (C+N) this was 83% Average duration was 3 5 (C) and 5 1 (C+N) weeks (p = 0 08, t-test) The accelerated schedule caused confluent mucositis in all but two cases (95%) with an average duration of 6 3 (C) and 6 7 (C+N) weeks Prolonged duration of confluent mucositis, i e persisting more than 6 weeks after the end of treatment, was observed in four patients after the accelerated regimen In all cases healing was complete within 3-4 months after treatment Tube feeding was needed in 29% of patients with oral cavity and oropharynx tumors and in 26% of patients with laryngeal and hypopharyngeal tumors with no significant differences between patients receiving carbogen alone and those receiving carbogen and nicotinamide Objective and functional mucosal reactions were not more severe for patients who received chemotherapy prior to irradiation (data not shown)

Addition of nicotinamide appeared to somewhat increase skin reactions The conventional schedule with carbogen caused moist desquamation in four of 16 patients (25%) and in 10 of 18 patients (56%) who received also nicotinamide (p = 0 06, Fisher's exact test) With the accelerated schedule this was nine of 16 (56%, C) and 15 of 23 (65%, C+N) Generally the skin healed rapidly within 3 weeks except in one case in which it required 7 weeks This patient was in the conventional schedule with carbogen and nicotinamide

Loco-regional tumor control All 39 patients with tumors of the larynx and hypopharynx who finished the planned course of irradiation had complete disappearance of loco-regional tumor at 6 weeks after the end of treatment Actuarial loco-regional control at one year was 86%, with 21 patients being in follow-up at least a year after treatment Thirty-two patients with oral cavity and oropharynx tumors completed the treatment, of whom 20 (63%) had complete regression of disease at 6 weeks The one-year actuarial loco-regional control rate for this group was 41%, with 23 patients in follow-up one year or more after treatment

Discussion

Carbogen breathing by the method described previously [14] appears to be feasible and well tolerated, even by patients with large tumors in the upper aero-digestive tract Only four of 74 patients were unable to cope with the procedure because they experienced sensations

of suffocation, in some cases with hyperventilation which is caused by the carbon dioxide component of the gas Polarographic O_2 measurements in metastatic lymph nodes from head and neck carcinomas showed that breathing time before optimal oxygenation was 4 min or less in 19 of 20 patients [20] It was also demonstrated that tumor pO_2 starts to decline after 12-18 min of carbogen breathing [4] Thus, irradiations are best delivered between 4 and 15 min after the start of carbogen breathing when tumor oxygenation is at its peak level This was accomplished in 92% of our radiation sessions

Reported side-effects of nicotinamide are nausea, vomiting, flushing, facial erythema, headache, fatigue, cutaneous reactions, and rare events of liver toxicity [29] Doses of nicotinamide of up to 6 g daily were described as reasonably safe and associated with a low incidence of side-effects In our experience, with doses of 6 g per day or 80 mg/kg per day, nausea and vomiting occurred frequently and necessitated discontinuation of the drug in 26% of patients Gastrointestinal symptoms were also reported in other clinical pilot studies three of six patients with head and neck cancer [30], two of six patients with breast cancer [23], and in two of 16 patients with malignant gliomas [28] The mechanism by which these symptoms are produced is not clear there may be a systemic effect or topical irritation of the gastrointestinal mucosa In the latter case, an alternative route of administration might reduce these unpleasant side-effects Severe renal dysfunction was associated with nicotinamide intake in two patients When this article was being finalized a third patient presented with this complication, also after previous treatment with cisplatin Thus, two patients received previous (cisplatin) and one concomitant (ACE-inhibitor, carbasalatcalcium) nephrotoxic medication This, in combination with decreased renal flow due to hypovolemia as a result of nicotinamide-induced vomiting and decreased oral fluid intake, may well be the cause of rapidly developing renal failure Any direct renal toxicity from nicotinamide can, however, not be excluded It was shown that the drug inhibits renal clearance of ^{51}CrEDTA and ^{125}I-iodohippurate in mice [10] These effects were dose-related and evident at doses from 400 mg/kg upwards which is considerably higher than the doses clinically applied Only one previous case of renal toxicity in man has been reported by Zackrisson et al [30] This patient received two daily doses of 6 and 3 g He had a known cardiomyopathy and was on treatment with an ACE-inhibitor as was one of our patients The patient had nausea and vomiting and developed hypotension with elevation of serum creatinine and liver enzymes The plasma concentrations of nicotinamide and its metabolites suggested that renal elimination was impaired Possibly in patients with compromised renal function (nephrotoxic medication, hypovolemia) nicotinamide accumulates in the plasma to a level at which it can aggravate renal dysfunction and may lead to severe renal failure

Unlike our experience with glioma patients [28], we did not observe nicotinamide-related hepatic toxicity in this category of head and neck cancer patients One of the patients with renal complications had moderate elevation of liver enzymes but this was unlikely to be related to nicotinamide intake because it started 2 weeks after discontinuation of the drug Apparently it was the combination with anti-epileptics and steroids that induced liver toxicity in the glioma patients

Nowadays with the availability of megavoltage equipment the incidence of severe skin reactions is low We previously reported an 8% rate of moist desquamation for conventional radiotherapy with total doses of 68-70 Gy [13] In this study we observed rates of 25% (C) and 56% (C+N) This increased skin reaction is not unexpected as enhancement ratios of 1 3-1 5 were estimated for rodent skin [17] With the accelerated schedule alone 50% of patients develop moist desquamation [13] When carbogen and nicotinamide are added there is only a small further increase to 56% (C) and 65% (C+N) which is not statistically significant Apart from one case, skin lesions healed rapidly The early reacting tissue of greater clinical significance is the mucosal membrane With the conventional schedule, 81% (C) and 83% (C+N) of patients in this study developed confluent mucositis of the oral cavity and oropharynx This corresponds to the 78% rate that we observed when these areas were treated with radiotherapy alone [15] Acceleration of treatment causes confluent mucositis in up to 90% of patients with laryngeal cancer, with complete healing within 6 weeks after completion of treatment in all cases [13] In this study confluent mucositis occurred in 95% of patients (C and C+N) However, four patients had healing times of up to 4 months A possible increase of severity of mucosal damage by addition of carbogen and nicotinamide may well be expressed as delayed recovery We believe that the acute radiation toxicity as observed with the current regimen is acceptable but we do not advocate further intensification of treatment as this might lead to non-healing lesions and consequential late effects

In conclusion, it is our opinion that radiotherapy combined with carbogen and nicotinamide is a safe treatment with manageable side-effects No expensive additional equipment is needed and it requires hardly any extra machine time Certain precautions should be taken, however, especially with regard to nicotinamide administration We recommend that nicotinamide should not be given to patients presenting with elevated serum creatinine levels and it should not be given concomitantly with nephrotoxic medication During treatment, renal function should be monitored at least once a week and twice weekly in patients at risk (e g those who were treated previously with cisplatin) Adequate oral intake is demanded When serum creatinine rises above normal levels, nicotinamide should

be discontinued immediately and proper hydration must be secured, if necessary by intravenous infusion.

Possibly, side-effects of nicotinamide can be limited when individual dose adjustments are made or when an alternative route of administration is used. Currently we are monitoring nicotinamide plasma levels in our patients to assess whether proper levels are obtained when treatment is given on a day to day routine basis and also to investigate if these are related to the observed side-effects.

Preliminary tumor control rates are promising and the approach offers potentials for larynx preservation. In the category of far advanced tumors proposed for palliative treatment, complete regressions were achieved and sustained in a significant proportion of the patients. We expect to increase the effectiveness of the treatment for this particular category with introduction of the accelerated schedule. Our experience with ARCON so far is encouraging and we will proceed with further clinical testing.

Acknowledgements

The authors would like to thank J. Liefers for excellent assistance with patient care and data management and J.F.M. Wetzels, Department of Medicine, Division of Nephrology, for advice.

References

1. Ang, K.K., Peters, L J., Weber, R.S et al. Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx. Int J. Radiat. Oncol. Biol. Phys. 19 1339-1345, 1990.

2. Brown, J M : Evidence for acute hypoxic cells in mouse tumours and a possible mechanism of reoxygenation. Br. J. Radiol. 52. 650-656, 1979

3. Chaplin, D.J., Durand, R.E and Olive, P.L Acute hypoxia in tumors: implication for modifiers of radiation effects. Int. J. Radiat Oncol. Biol. Phys. 12: 1279-1282, 1986

4. Falk, S.J., Ward, R. and Bleehen, N.M The influence of carbogen breathing on tumour tissue oxygenation in man evaluated by computerised pO_2 histography. Br J. Cancer 66· 919-924, 1992.

5. Gatenby, R A., Kessler, H.B., Rosenblum, J S. et al. Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radiation therapy. Int. J. Radiat. Oncol Biol. Phys. 14: 831-838, 1988.

6 Haustermans, K., van der Kogel, A J., Vanacker, B and van der Schueren, E Influence of combined use of nicotinamide and carbogen on rat spinal cord radiation tolerance. Radiother Oncol. 31: 123-128, 1994.

7. Henk, J M Late results of a trial of hyperbaric oxygen and radiotherapy in head and neck cancer: a rationale for hypoxic cell sensitizers? Int J. Radiat. Oncol. Biol. Phys 12: 1339-1341, 1986

8 Henk, J M., Kunkler, P.B. and Smith, C W Radiotherapy and hyperbaric oxygen in head and neck cancer. Lancet ii. 101-103, 1977.

9 Höckel, M., Knoop, C., Schlenger, K. et al Intratumoral pO_2 predicts survival in advanced cancer of the uterine cervix Radiother. Oncol 26 45-50, 1993

10. Honess, D.J. and Bleehen, N.M. Effects of the radiosensitising agent nicotinamide on relative tissue perfusion and kidney function in C3H mice Radiother. Oncol 27. 140-148, 1993.

11. Horsman, M.R., Chaplin, D J. and Brown, J M Tumor radiosensitization by nicotinamide: a result of improved perfusion and oxygenation. Radiat Res 118: 139-150, 1989

12. International Commission on Radiation Units and measurements: Dose specification for reporting external beam therapy with photons and electrons. Report 29. ICRU Publications, Washington, DC, 1978.

13. Kaanders, J.H.A.M., van Daal, W.A.J., Hoogenraad, W.J. and van der Kogel, A.J. Accelerated fractionation radiotherapy for laryngeal cancer, acute and late toxicity. Int. J. Radiat. Oncol. Biol. Phys. 24: 497-503, 1992.

14. Kaanders, J.H.A.M. and van der Maazen, R.W.M. A convenient and reliable method for carbogen breathing in man. Radiother. Oncol. 29: 341-343, 1993.

15. Kaanders, J.H.A.M., Pop, L.A.M., Muytjens, H.L., Bruaset, I. and van Daal, W.A.J. Topical administration of antimicrobial agents to prevent irradiation mucositis of the oral cavity and oropharynx: a pilot study. Radiat. Oncol. Invest. 2: 283-290, 1995.

16. Kelleher, D.K. and Vaupel, P.W. Nicotinamide exerts different acute effects on microcirculatory function and tissue oxygenation in rat tumors. Int. J. Radiat. Oncol. Biol. Phys. 26: 95-102, 1993.

17. Kjellen, E., Joiner, M.C., Collier, J.M., Johns, H. and Rojas, A. A therapeutic benefit from combining normobaric carbogen or oxygen with nicotinamide in fractionated X-ray treatments. Radiother. Oncol. 22: 81-91, 1991.

18. Lartigau, E., Le Ridant, A.-M., Lambin, P. et al. Oxygenation of head and neck tumors. Cancer 71: 2319-2325, 1993.

19. Lartigau, E., Vitu, L., Haie-Meder, C. et al. Feasibility of measuring oxygen tension in uterine cervix carcinoma. Eur. J. Cancer 28A: 1354-1357, 1992.

20. Martin, L., Lartigau, E., Weeger, P. et al. Changes in the oxygenation of head and neck tumors during carbogen breathing. Radiother. Oncol. 27: 123-130, 1993.

21. Overgaard, J., Hansen, H.S., Andersen, A.P. et al. Misonidazole combined with split-course radiotherapy in the treatment of invasive carcinoma of larynx and pharynx: report from the DAHANCA 2 study. Int. J. Radiat. Oncol. Biol. Phys. 16: 1065-1068, 1989.

22. Overgaard, J., Sand Hansen, H., Lindeløv, B. et al. Nimorazole as a hypoxic radiosensitizer in the treatment of supraglottic larynx and pharynx carcinomas. First

report from the Danish Head and Neck Cancer Study (DAHANCA) protocol 5-85 Radiother Oncol 20 (Suppl 1) 143-149, 1991

23 Pigott, K , Dische, S and Saunders, M I The addition of carbogen and nicotinamide to a palliative fractionation schedule for locally advanced breast cancer Br J Radiol 68 215-218, 1995

24 Rojas, A Radiosensitization with normobaric oxygen and carbogen Radiother Oncol 20 (Suppl 1) 65-70, 1991

25 Rojas, A , Joiner, M C and Denekamp, J Extrapolations from laboratory and preclinical studies for the use of carbogen and nicotinamide in radiotherapy Radiother Oncol 24 123-124, 1992

26 Saunders, M I , Dische, S , Grosch, E J et al Experience with CHART Int J Radiat Oncol Biol Phys 21 871-878, 1991

27 Thomlinson, R H and Gray, L H The histological structure of some human lung cancers and the possible implications for radiotherapy Br J Cancer 9 539-549, 1955

28 Van der Maazen, R W M , Thijssen, H O M , Kaanders, J H A M et al Conventional radiotherapy combined with carbogen breathing and nicotinamide for malignant gliomas Radiother Oncol 35 118-122, 1995

29 Zackheim, H S , Vasily, D B , Westphal, M L and Hastings, C W Reactions to niacinamide J Am Acad Dermatol 4 736-737, 1981

30 Zackrisson, B , Franzén, L , Henriksson, R et al Acute effects of accelerated radiotherapy in combination with carbogen breathing and nicotinamide (ARCON) Acta Oncol 33 377-381, 1994

CHAPTER 6

ADMINISTRATION OF NICOTINAMIDE DURING A FIVE- TO SEVEN-WEEK COURSE OF RADIOTHERAPY: PHARMACOKINETICS, TOLERANCE, AND COMPLIANCE

Johannes H.A.M. Kaanders

Michael R.L. Stratford

Janine Liefers

Madeleine F. Dennis

Albert J. van der Kogel

Willem A.J. van Daal

Anamaria Rojas

Reprinted from: Radiother. Oncol. 43: 67-73, 1997

with permission from Elsevier Science

Abstract

Nicotinamide was administered daily as a liquid formulation to head and neck cancer patients receiving a 5- to 7-week course of radiotherapy The pharmacokinetics, compliance, and tolerance of this drug formulation were studied.

Blood samples were drawn and nicotinamide levels determined in 40 head and neck cancer patients On the first treatment day serial samples were obtained followed by daily samples at the time of irradiation during the first and last full weeks of the treatment Side-effects of nicotinamide were monitored.

In all patients peak concentrations greater than 700 nmol/ml could be obtained 0.25-3 h (mean· 0 83 ± 0 73 h) after drug intake. During the first week of treatment plasma levels at the time of irradiation were adequate in 82% of the samples. This decreased to 59% in the last week of treatment which can be partly attributed to reduced compliance. The most important side-effect of nicotinamide was nausea with or without vomiting occurring in 65% of the patients. Severe side-effects were associated with high plasma concentrations over subsequent days. Tolerance improved after a 25% reduction of the dose in six of seven patients but plasma levels at the time of irradiation fell below 700 nmol/ml in four out of six of these patients.

In conclusion, peak plasma concentrations above the 700 nmol/ml level were obtained in all patients but these concentrations could not be reproduced during the entire course of the treatment in a significant portion of the subjects. Side-effects of nicotinamide are associated with plasma concentrations and tolerance can be improved by a moderate reduction of dose

Introduction

Nicotinamide is currently being assessed in clinical trials as a modifier of acute perfusion-limited tumor-hypoxia This compound can reduce the intermittent closure of blood vessels in experimental rodent tumors [2, 7] and consequently decrease hypoxic-cell radioresistance [6, 10] In addition, nicotinamide has been shown to enhance the sensitizing effect of carbogen [1, 12, 13], which overcomes the sparing effect of chronic diffusion-limited hypoxia [16] With fractionated radiation schedules to mouse tumors, relative to radiation treatments in air without the drug, enhancement ratios in the order of 1 3-1 9 have been obtained for the combination of carbogen and nicotinamide [3, 12, 14, 15] Experimentally, plasma levels of 700 nmol/ml of nicotinamide are required at the time of irradiation to obtain a sensitizing effect [8, 15] Initial studies in healthy human volunteers showed that peak plasma levels of 800-1600 nmol/ml could be obtained after oral intake of 6 g [8, 19] Horsman et al showed that for maximal radiosensitization tumors should be irradiated at the time of peak drug levels [8]

The current clinical practice is to prescribe the drug on a weight adjusted basis and adequate plasma levels can be obtained in patients with oral doses of 80 mg/kg per day [9, 18] In a recent study performed on a small number of patients undergoing CHART and given this dose of nicotinamide over 12 consecutive days, the drug was well tolerated but large inter-patient variations were seen both with regard to the maximum plasma concentration (C_{max}) obtained and the time taken to reach this peak (T_{max}) Peak levels were reported to range from 400 to 1400 nmol/ml with T_{max} values from 0 8 to 4 h, but in the four patients in which repeated assessments were made at various times during the course of radiotherapy the kinetic parameters were reproducible [9] However, there are no reliable pharmacokinetic and toxicity data with prolonged daily administration of high doses of nicotinamide during a 5- to 7-week course of radiotherapy and information on patient compliance is also lacking

Although nicotinamide was suggested as a relatively non-toxic agent with a low incidence of side-effects even at the dose levels required for tumor radiosensitization [20], in our experience gastrointestinal complaints occur frequently In a previous study 60% and 36% of the patients had nausea and vomiting, respectively, and in 26% this was reason to discontinue drug intake [11] Till now clinical studies have failed to demonstrate a relationship between side-effects and nicotinamide plasma levels [18]

We therefore decided to investigate if adequate nicotinamide plasma levels could be obtained in head and neck cancer patients enrolled in a study combining radiotherapy with carbogen breathing and nicotinamide and whether such levels were maintained throughout

the course of treatment. We also aimed to study whether the use of a liquid formulation of the drug improves the pharmacokinetic parameters of C_{max} and/or T_{max} and whether there is a relationship between plasma levels and the incidence and severity of toxic side-effects. This paper reports on data obtained in 40 patients undergoing either conventional or accelerated radiotherapy.

Materials and Methods

Patients: In our institute head and neck cancer patients with stage III-IV disease and also stage II hypopharyngeal cancer are currently being enrolled in a study combining radiotherapy with carbogen breathing and nicotinamide, details of which have been described previously [11]. Inclusion criteria are an age over 18 years, WHO performance status of 0-2, no severe heart or lung disease, no severe liver or kidney dysfunction, no severe stridor, no distant metastases, and written informed consent. From February 1995 to March 1996, after approval from the local ethical committee, 40 consecutive patients consented to have plasma samples drawn for determination of nicotinamide levels. There were 28 men and 12 women. Mean age was 61 years with a range of 41-82 years.

Radiotherapy: Nine patients were treated by a conventional schedule and 31 by an accelerated fractionation schedule. Conventional radiotherapy was given in fractions of 2 Gy, five times a week to a total dose of 68 Gy. Overall treatment time was 46-48 days. With the accelerated schedule the total dose was 64-68 Gy while dose per fraction remained the same and treatment time was reduced by 10 days by giving two fractions per day during the last 1.5 weeks of the treatment. The interval between the two fractions per day was 6 h. Some patients were hospitalized when they were treated twice daily because of travelling distance.

Nicotinamide administration: Nicotinamide (Pharmachemie, Haarlem, The Netherlands), dissolved in fruit juice was administered orally 1.5 h before irradiation. After the pharmacokinetic data of the first 22 patients were analyzed, the interval was changed to 1 h for the following 18 patients. A light meal, if taken at least 1 h before drug intake, was allowed. On days when two fractions were given, only one dose of nicotinamide was administered before the first treatment. The daily dose was 80 mg/kg to a maximum of 6 g. Since November 1995 a dose reduction to 60 mg/kg was introduced for patients with severe side-effects. Sixteen patients have been treated with this approach. If a dose reduction was

applied, nicotinamide was discontinued during one day prior to this to allow complete elimination of the drug in case accumulation had occurred

Sample acquisition and analysis of nicotinamide concentrations On the first treatment day serial samples were taken usually through an intravenous cannula inserted in the arm An initial 5 ml of blood was discarded before the actual sample was collected On subsequent days blood was drawn by way of a venous puncture Five-ml samples were collected in heparinized tubes and immediately stored at 4°C Plasma was separated by centrifugation (3000 x *g*, 10 min) within 8 h of sampling and then stored at -20°C prior to analysis Nicotinamide concentrations were determined in methanol extracts of plasma using high performance liquid chromatography [17] From all patients a full profile was obtained on the first day of treatment Sampling times on the first day were at 0, 0 25, 0 5, 1, 1 5, 2, 3, 4, 6, and 12 h after nicotinamide ingestion and the residual level was measured after 24 h (C_{res}) One or 1 5 h after intake of the second dose another sample was collected Because of the frequent sampling on these first 2 days, patients were hospitalized during this time Thereafter samples were obtained daily during the first and last full weeks of the treatment at the time of irradiation, i e 1 or 1 5 h after nicotinamide intake In addition, if nicotinamide dose was reduced, plasma samples were collected on at least 3 consecutive days starting on the first day of dose reduction

Monitoring during treatment At each time of sampling blood pressure and heart rate were recorded During the course of treatment the patients were seen by both the attending radiation oncologist and, separately, by the research assistant at least once a week and more frequently if necessary, e g when side-effects occurred The patients were asked if any adverse events had occurred and they were specifically asked if they had experienced nausea and/or vomiting If they reported vomiting they were asked to specify when this occurred and how often Anti-emetics (metoclopramide, ondansetron) were prescribed when necessary Side-effects of nicotinamide were considered severe if they led to a discontinuation of the drug or a reduction of the daily dose Gastrointestinal bleeding in one patient and renal dysfunction in another patient were felt to be possibly related to nicotinamide and also scored as severe

Statistics For each patient the plasma levels obtained at the time of irradiation during the first full week were plotted and a linear least-squares regression fit was done If there was a positive and significant ($p < 0\ 05$) correlation of plasma levels with time, the patient was considered to accumulate nicotinamide with daily administration A discriminant

analysis was done to examine which pharmacokinetic parameters predicted best for nicotinamide toxicity All statistical analyses were done on a Macintosh computer using the Statistica 4 0 software package

Results

Tolerance The reported side-effects are listed in Table 1 Nausea with or without vomiting was reported by 65% of the patients Often these complaints were unresponsive to anti-emetics including ondansetron Eight patients experienced no side-effects at all while 16 patients had side-effects that were considered as severe Nine patients discontinued nicotinamide intake because of side-effects, eight because of nausea and one because of renal toxicity Five patients discontinued intake of the drug for other reasons three patients went off study because of very poor compliance with the treatment protocol, one patient stopped nicotinamide in the fourth week of treatment because of the poor taste and dysphagia due to irradiation-mucositis, and in one case it was decided to stop at day 4 because of pre-existent renal disturbances Of the 16 patients treated since November 1995, seven had a dose reduction to 60 mg/kg because of severe nausea Only one of these 16 patients finally discontinued nicotinamide intake because of the side-effects in contrast to eight of the 19 patients treated previously (excluding the five patients that stopped nicotinamide for other reasons)

There was no indication of an effect of nicotinamide on blood pressure or pulse

Table 1. *Nicotinamide side-effects in 40 patients*

Side-effect	No. of patients
nausea	26
vomiting	13
flushing	7
dizziness	6
epigastric pain	3
gastrointestinal bleeding	1
renal dysfunction	1
emotional disturbances	1

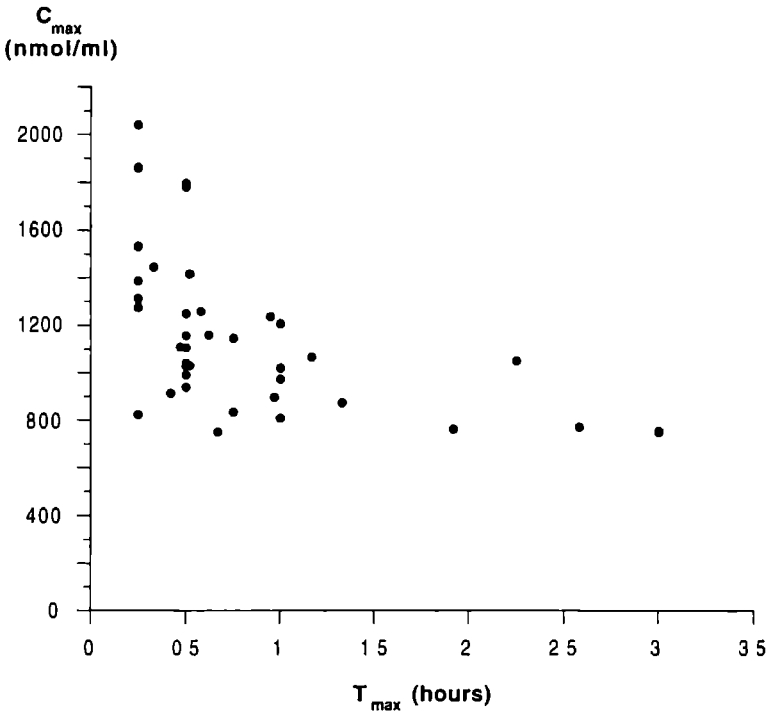


Fig. 1. *Scatterplot of C_{max} versus T_{max} including all 40 patients*

First day nicotinamide plasma profile· C_{max} and T_{max} for each individual are shown in Fig. 1 Mean and median C_{max} were 1154 nmol/ml and 1088 nmol/ml with a standard deviation (SD) of ± 326 nmol/ml and a range of 752-2041 nmol/ml Thus, in all patients a minimal level of 700 nmol/ml could be obtained Mean and median T_{max} were 0 83 h and 0 51 h (SD ± 0 73 h, range 0.25-3 h) T_{max} was equal or less than 1 h in 33 of the 40 cases Fig. 2 illustrates the mean of the pharmacokinetic profiles obtained on the first day of treatment of all 40 patients The profiles of two individual patients are added in the figure to illustrate the inter-individual variability which is largest during the first hour after nicotinamide intake One patient has a very high C_{max} with short T_{max} whereas the other has a relatively low C_{max} and long T_{max}. With the accelerated radiation schedule the second treatment of the day is given 7-8 h after nicotinamide intake at which time the interpolated mean plasma level was about 500 nmol/ml Mean and median C_{res} were 66 nmol/ml and 53 nmol/ml (SD ± 62 nmol/ml, range 0-221 nmol/ml)

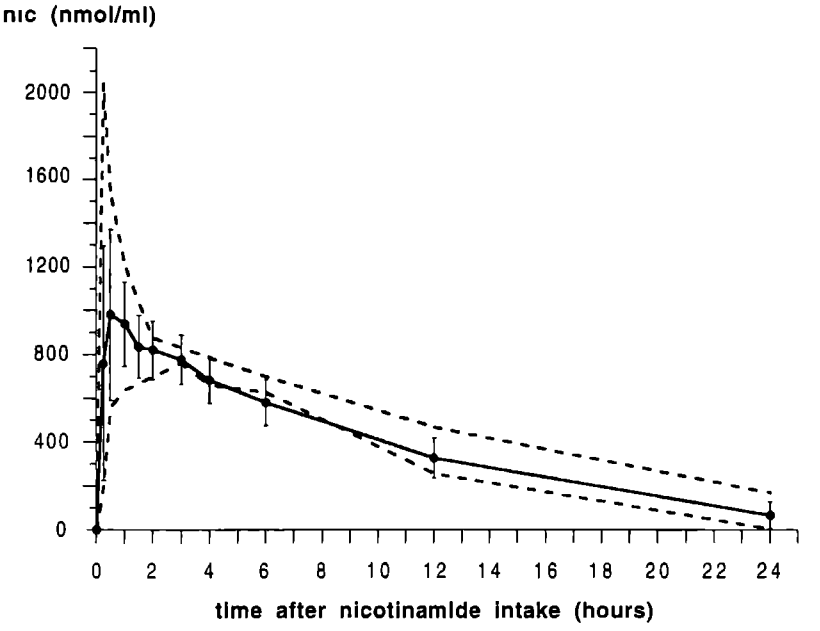


Fig. 2. *Nicotinamide (nic) plasma concentrations as a function of time after intake Mean of 40 patients with standard deviations The dotted lines represent two individual patients one with high C_{max} and short T_{max} and the other with low C_{max} and long T_{max}*

Nicotinamide plasma levels during first and last weeks of treatment Fig 3 shows the individual and mean plasma levels at the time of irradiation during the first and last full weeks of the treatment Some patients started radiotherapy on a Thursday, in those cases nicotinamide levels were determined in the first full week but also on the first 2 treatment days before and these are also shown in the figure Nicotinamide levels measured after dose reduction are not included At the start of the treatment 179 of 219 values (82%) were above the desired 700 nmol/ml and nine of 40 patients had lower values more than once In 11 of 37 patients a linear least-squares regression fit to the values obtained at the time of irradiation during the first full week indicated that accumulation of nicotinamide occurred with daily administration In three cases the regression analysis could not be carried out because drug intake was already discontinued in the first week Accumulation was not correlated with C_{res}, i e patients with a relatively high residual 24-h level after the first drug dose did not necessarily show drug accumulation

On average, plasma concentrations decreased towards the end of the treatment During the last week 55 of 94 (59%) values were above the 700 nmol/ml level and nine of the 19 patients who continued nicotinamide intake until the end of the treatment and without a dose reduction had values that fell below this level more than once

Fig 4 shows the nicotinamide plasma concentrations for the seven patients who had a dose reduction. It includes the levels obtained in the first week with doses of 80 mg/kg, the levels directly after reduction to 60 mg/kg, and those obtained in the last week of the treatment. One patient continued having severe side-effects and stopped nicotinamide intake In two patients levels greater than 700 nmol/ml were obtained and reproduced daily with the 60 mg/kg dose, three others produced levels in the 400-700 nmol/ml range, and in one

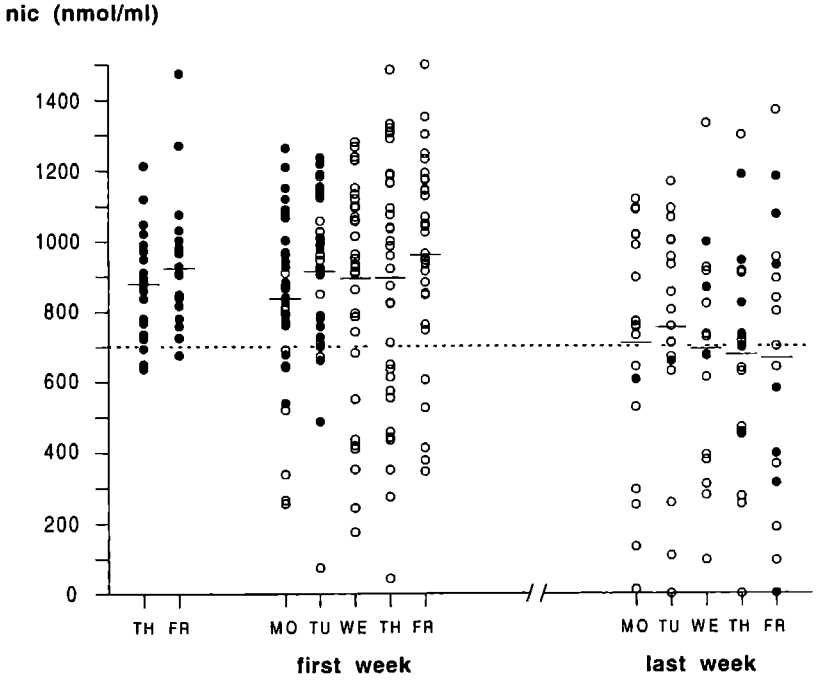


Fig. 3. *Nicotinamide plasma concentrations at the time of irradiation during the first and last week of the treatment. Individual values of 40 patients are represented by the circles. Closed and open symbols represent values obtained during hospitalization and at the outpatients' department respectively. Horizontal bars indicate mean values. Dashed horizontal line indicates 700 nmol/ml level.*

patient the levels were clearly inadequate which, we believe, was largely due to poor compliance In fact this patient had already insufficient levels at the beginning of the treatment

Correlation between nicotinamide side-effects and plasma levels Adequate assessment of the severity of side-effects was not possible in five cases three patients were taken out of the study because of very poor compliance with the treatment protocol, in one case it was decided to stop at day 4 because of pre-existing renal disturbances, and in one case reporting of side-effects was very inconsistent and unreliable and therefore not interpretable Thus, 35

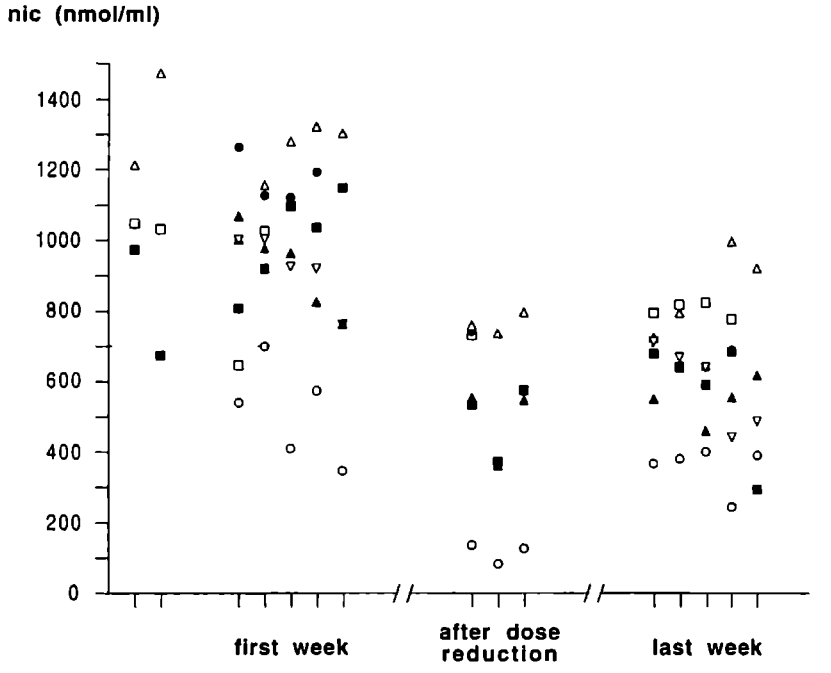


Fig. 4. *Nicotinamide plasma concentrations at the time of irradiation in seven patients Data obtained before dose reduction (first week), on 3 consecutive days directly after dose reduction, and during the last week of treatment Different symbols represent different patients (open circle patient with assumed poor compliance, closed circle patient discontinued nicotinamide intake) Dashed horizontal line indicates 700 nmol/ml level*

patients were evaluable for this analysis of which 16 patients experienced side-effects that were considered as severe. We investigated if the pharmacokinetic parameters could predict for nicotinamide toxicity by discriminant analysis. The following parameters were included: absolute daily dose, C_{max}, area under the curve (AUC) derived from the first day profile, C_{res}, the mean of the plasma concentrations measured at the time of irradiation during the first week (C_{mean}), and whether or not accumulation occurred. There was no correlation between side-effects and absolute daily dose or C_{res} or AUC. High C_{max} ($p = 0.03$) and high C_{mean} ($p = 0.008$) were correlated with the occurrence of severe side-effects. There was a positive correlation between drug accumulation and severe side-effects but this did not reach statistical significance ($p = 0.10$). Eight of the 11 patients who showed drug accumulation had severe side-effects as compared to seven of the 23 patients in whom there was no indication of accumulation. The most powerful single predictor for severe nicotinamide toxicity was C_{mean} (Fig. 5).

Discussion

Tolerance: Gastrointestinal symptoms, flushing, dizziness, sweating, fatigue, and headache were already recognized as side-effects of nicotinamide [5, 8, 9, 20]. In a previous report we associated renal failure with nicotinamide intake as a relatively infrequent event but one that can have serious consequences [11]. In our total experience this occurred in three of 61 patients that were treated with nicotinamide. All three had received nephrotoxic medication previously (cisplatin) or concomitantly (ACE-inhibitor, carbasalatcalcium). Consequently we withheld nicotinamide in patients with pre-existing renal dysfunction and it was not administered concomitantly with nephrotoxic medication. Since then we have treated 41 other patients and no renal toxicity has been observed. One patient had a gastric bleeding. He also used carbasalatcalcium for analgesia which is a salicylate and known to cause gastric irritation which may have been enhanced by nicotinamide. One patient reported emotional lability and depressive moods. This was also noted in another patient treated previously. It remains unclear whether this relates to nicotinamide use.

The most frequent adverse effect is nausea with or without vomiting. With prolonged daily administration it occurred in 65% of the patients and was often unresponsive to anti-emetics confirming the findings from our previous study [11]. In 14 patients drug intake was either discontinued or the dose was reduced because these symptoms were severe and we did not allow these side-effects to significantly interfere with nutritional intake as this

was already impaired in most of our patients We observed a significant correlation between side-effects and some pharmacokinetic parameters In particular high plasma concentrations over subsequent days are associated with severe side-effects whereas absolute daily dose

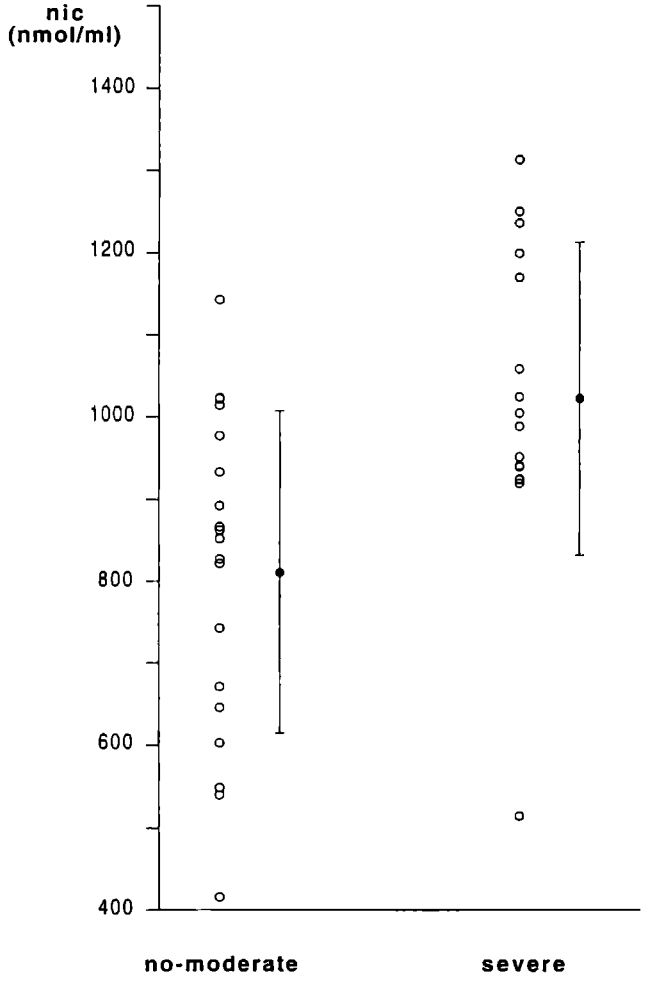


Fig. 5. *Mean of nicotinamide plasma concentrations measured at the time of irradiation during the first week of treatment Open symbols represent mean per patient (35 patients) Patients are divided in two groups by severity of nicotinamide side-effects (no-moderate versus severe) Closed symbols indicate mean values of the two groups with standard deviations*

was not This indicates that, apart from direct topical irritation of the gastrointestinal mucosa, there is probably also a systemic effect Thus, alternative routes of drug administration may not circumvent the problem of nausea

Severe clinical effects were reported with daily doses higher than 6 g or 80 mg/kg administered over a few subsequent days [4, 9] This was associated with high residual 24-h plasma levels and significant drug accumulation It was suggested that accumulation can become of a particular concern when residual levels are higher than 300 nmol/ml [9] With the 80 mg/kg dose we observed relatively low residual values after the first drug intake (mean 66 nmol/ml) which did not predict for accumulation or side-effects

C_{max} and T_{max} The nicotinamide plasma profiles obtained on the first treatment day show that, with a dose of 80 mg/kg, adequate (> 700 nmol/ml) levels could be obtained in all patients Large inter-patient variations in C_{max} were seen however We used a liquid formulation which, on average, produced higher peak levels than tablets which were used in other studies [9, 19] and also shorter T_{max} with a mean of 0 83 h (SD ± 0 73) as compared to 2 1 h (SD ± 1 3) with tablets [9] Apparently the drug is more rapidly absorbed when administered as a liquid formulation resulting in higher C_{max} Initially, irradiations were given 1 5 h after drug intake but when an interim-analysis showed this short T_{max}, the interval was reduced to 1 h Eighty-three per cent (33/40) of the patients had $T_{max} \leq 1$ h and the inter-patient variability was less than with tablets which can be of advantage for the timing of irradiations It has been suggested that absorption is also more rapid with higher peak concentrations when the drug is taken on an empty stomach [8, 9] Our patients were allowed to take a light meal at least 1 h before drug intake We found it not advisable for them to skip or postpone meals as most have impaired nutritional intake because of the location of the tumor and, as treatment progresses, because of radiation mucositis

Compliance On the first 2 treatment days, when patients were hospitalized and nicotinamide was ingested in the presence of the nurse who was to obtain the plasma sample, nicotinamide levels at the time of irradiation were nearly always adequate With progression of treatment there was an increasing proportion of values below 700 nmol/ml with some being very low or even zero During the last week of the treatment nine of the 19 patients who continued nicotinamide intake until the end of the treatment and without a dose reduction had repeatedly low values at the time of irradiation In some but not all cases this could be explained because the patient vomited shortly after nicotinamide intake. Alternatively, repeated administration of nicotinamide might possibly activate metabolic pathways resulting in a more rapid elimination of the drug However, full kinetic profiles

obtained in patients administered the same dose of nicotinamide daily, albeit over 12 days, showed no indication of this [9] Furthermore, together with nicotinamide concentrations, we measured the plasma levels of the three major metabolites of nicotinamide (1-methyl nicotinamide, nicotinamide N-oxide, and 2-pyridones) in our patients at the start of treatment and 5-7 weeks later (data not shown) The metabolite levels gave no indication of a faster elimination of the drug with time, i e low levels of nicotinamide correspond with low levels of metabolites We must therefore assume a decreased compliance, i e patients were not always taking the dose of nicotinamide they were supposed to This may well be caused by the experience of side-effects and the bad taste which is a disadvantage of the liquid formulation An additional argument is the often weak psychosocial status of head and neck cancer patients with inadequate self-care including poor drug compliance Other patient categories may do better in this respect

Dose reduction The high mean plasma concentrations shown in Fig 5 suggest that a moderate dose reduction for those patients with severe adverse effects might still produce adequate plasma levels All but one had mean plasma levels greater than 900 nmol/ml at the time of irradiations It was shown that peak plasma levels are linearly dependent on the administered drug dose [8, 18, 19] If levels of at least 900 nmol/ml can be obtained with 80 mg/kg, the expected minimum level after a 25% reduction of dose would be around 700 nmol/ml or slightly lower We introduced a dose reduction to 60 mg/kg for patients who experienced severe nausea and/or intractable vomiting Tolerance improved after this moderate reduction of dose in six of seven patients and they were able to continue nicotinamide intake until the end of the treatment In five patients indeed plasma concentrations of about 75% of the initial values were obtained on some days but in only two patients this could be reproduced daily This is probably not attributable to the reduced drug dose only but also to a reduced compliance as was argued above Possibly, when the lower dose is administered from the start of treatment, better tolerance may also lead to improved compliance

In rodent tumors, nicotinamide plasma levels between 700-1000 nmol/ml achieve significant increases in radiosensitization over that of carbogen alone [14] In this current study we have demonstrated that these levels can be achieved in man with oral doses of 80 mg/kg but it is not always possible to reproduce such levels daily during a fractionated radiation treatment Lower doses may improve tolerance and compliance but the question arises whether such doses can produce drug levels sufficient for significant radiosensitization Further studies in experimental tumors are needed to determine the lower threshold dose for radiosensitization by nicotinamide It may also be helpful to obtain a

pharmacokinetic profile from each patient over the first 2 h after nicotinamide intake prior to the start of treatment for optimal timing such that patients are irradiated as close to their individual T_{max} as possible. It has been shown that, with repeated drug administrations, the intra-patient variations of T_{max} are small [9].

Conclusions: A nicotinamide dose of 80 mg/kg administered as a liquid formulation can produce peak plasma concentrations above the 700 nmol/ml level in all patients. Equivalent levels have been shown to be sufficient for radiosensitization in mice. However, due to adverse effects and loss of compliance, these concentrations could not be reproduced during the full course of the 5- to 7-week treatment in a significant portion of the subjects. High plasma concentrations over subsequent days are associated with severe side-effects and a 25% dose reduction can improve tolerance. The question remains whether drug concentrations obtained after such dose reduction are still effective. Timing of irradiations may become more critical with the lower dose and further studies are needed to assess the threshold dose for radiosensitization by nicotinamide.

References

1. Chaplin, D.J., Horsman, M.R. and Aoki, D.S. Nicotinamide, Fluosol DA and carbogen: a strategy to reoxygenate acutely and chronically hypoxic cells in vivo. Br. J. Cancer 63: 109-113, 1991.

2. Chaplin, D.J., Horsman, M.R. and Trotter, M.J. The effect of nicotinamide on the microregional heterogeneity of oxygen delivery within a murine tumour. J. Natl. Cancer Inst. 82: 672-676, 1990.

3. Dorie, M.J., Menke, D. and Brown, J.M. Comparison of the enhancement of tumor responses to fractionated irradiation by SR 4233 (tirapazamine) and by nicotinamide with carbogen. Int. J. Radiat. Oncol. Biol. Phys. 28: 145-150, 1994.

4. Dragovic, J., Kim, S.H., Brown, S.L. and Kim, J.H. Nicotinamide pharmacokinetics in patients. Radiother. Oncol. 36: 225-228, 1995.

5. Hoffer, A. Safety, side effects and relative lack of toxicity of nicotinic acid and nicotinamide. Schizophrenia 1: 78-87, 1969.

6. Horsman, M.R., Brown, D.M., Lemmon, M.J., Brown, J.M. and Lee, W.W. Preferential tumor radiosensitization by analogs of nicotinamide and benzamide. Int. J. Radiat. Oncol. Biol. Phys. 12: 1307-1310, 1986.

7. Horsman, M.R., Chaplin, D.J. and Overgaard, J. Combination of nicotinamide and hyperthermia to eliminate radioresistant chronically and acutely hypoxic tumour cells. Cancer Res. 50: 7430-7436, 1990.

8. Horsman, M.R., Høyer, M., Honess, D.J., Dennis, I.F. and Overgaard, J. Nicotinamide pharmacokinetics in humans and mice: a comparative assessment and the implications for radiotherapy. Radiother. Oncol. 27: 131-139, 1993.

9. Hoskin, P.J., Stratford, M.R.L., Saunders, M.I., Hall, D.W., Dennis, M.F. and Rojas, A. Administration of nicotinamide during CHART: pharmacokinetics, dose escalation, and clinical toxicity. Int. J. Radiat. Oncol. Biol. Phys. 32: 1111-1119, 1995.

10. Jonsson, G.G., Kjellen, E., Pero, R.W. and Cameron, R. Radiosensitization effects of nicotinamide on malignant and normal mouse tissue. Cancer Res. 45: 3609-3614, 1985.

11. Kaanders, J.H.A.M., Pop, L.A.M., Marres, H.A.M., van der Maazen, R.W.M., van der Kogel, A.J. and van Daal, W.A.J. Radiotherapy with carbogen breathing and nicotinamide in head and neck cancer: feasibility and toxicity. Radiother. Oncol. 37: 190-198, 1995.

12. Kjellen, E., Joiner, M.C., Collier, J.M., Johns, H. and Rojas, A. A therapeutic benefit from combining normobaric carbogen or oxygen with nicotinamide in fractionated X-ray treatments. Radiother. Oncol. 22: 81-91, 1991.

13. Rojas, A. Radiosensitization with normobaric oxygen and carbogen. Radiother. Oncol. 20 (Suppl. 1): 65-70, 1991.

14. Rojas, A., Hirst, V.K., Calvert, A.S. and Johns, H. Carbogen and nicotinamide as radiosensitizers in a murine mammary carcinoma using conventional and accelerated radiotherapy. Int. J. Radiat. Biol. Oncol. Phys. 34: 357-365, 1996.

15. Rojas, A., Hodgkiss, R.J., Stratford, M.R.L., Dennis, M.F. and Johns, H. Pharmacokinetics of varying doses of nicotinamide and tumour radiosensitisation with carbogen and nicotinamide: clinical considerations. Br. J. Cancer 68: 1115-1121, 1993.

16. Rojas, A., Joiner, M.C., Hodgkiss, R.J., Carl, U., Kjellen, E. and Wilson, G.D. Enhancement of tumor radiosensitivity and reduced hypoxia-dependent binding of a 2-nitroimidazole with normobaric oxygen and carbogen: a therapeutic comparison with skin and kidneys. Int. J. Radiat. Biol. Oncol. Phys. 23: 361-366, 1992.

17. Stratford, M.R.L. and Dennis, M.F. High-performance liquid chromatographic determination of nicotinamide and its metabolites in human and murine plasma and urine. J. Chromatogr. 582: 145-151, 1992.

18. Stratford, M.R., Dennis, M.F., Hoskin, P., Saunders, M.I., Hodgkiss, R.J., Rojas, A. Nicotinamide pharmacokinetics in normal volunteers and patients undergoing palliative radiotherapy. Acta Oncol. 35: 213-219, 1996.

19. Stratford, M.R.L., Rojas, A., Hall, D.W. et al. Pharmacokinetics of nicotinamide and its effect on blood pressure, pulse and body temperature in normal human volunteers. Radiother. Oncol. 25: 7-42, 1992.

20. Zackheim, H.S., Vasily, D.B., Westphal, M.L. and Hastings, C.W. Reactions to niacinamide. J. Am. Acad. Dermatol. 4: 736-737, 1981.

CHAPTER 7

ACCELERATED RADIOTHERAPY WITH CARBOGEN AND NICOTINAMIDE (ARCON) FOR LARYNGEAL CANCER

Johannes H.A.M. Kaanders

Lucas A.M. Pop

Henri A.M. Marres

Janine Liefers

Franciscus J.A. van den Hoogen

Willem A.J. van Daal

Albert J. van der Kogel

Reprinted from: Radiother. Oncol. 48: 115-122, 1998

with permission from Elsevier Science

Abstract

Tumor hypoxia and tumor cell repopulation are known factors determining radiation response Accelerated radiotherapy as a method to counteract cellular repopulation was combined with carbogen (95% O_2 + 5% CO_2) breathing and oral administration of nicotinamide as a means to improve tumor perfusion and oxygenation The feasibility, toxicity and clinical effectiveness of this approach as voice preserving treatment for carcinoma of the larynx was assessed in a prospective study

Sixty-two patients with stage III-IV laryngeal carcinoma were treated with a schedule of accelerated radiotherapy Total radiation dose to the primary tumor was 64 Gy and that to the metastatic nodes was 68 Gy delivered in fractions of 2 Gy over 35-37 days Radiotherapy was combined with carbogen breathing in the initial 11 patients and with both carbogen and nicotinamide administration in the subsequent 51 patients

After a median follow-up of 24 months, the actuarial local control rate at 2 years was 92% This is higher than any previous report in the literature for this category of patients Five patients had a local tumor recurrence and underwent laryngectomy There was one regional recurrence Including salvage surgery the loco-regional control rate was 100% Four patients developed distant metastases and died The actuarial overall survival rate at 2 years was 85% Toxicity was increased relative to conventional radiotherapy but was considered as acceptable One patient underwent laryngectomy for radiation-induced cartilage necrosis

These preliminary results indicate that advanced laryngeal cancer can be controlled in a high proportion of patients when treated with accelerated radiotherapy combined with carbogen and nicotinamide This approach offers excellent possibilities for larynx preservation

Introduction

It is a common clinical experience that some malignant tumors are highly curable by radiotherapy while others are not Major biological factors determining the radiation response of tumors include intrinsic radiosensitivity and DNA repair capacity, proliferative activity of clonogenic tumor cells and the tumor oxygenation status The radiosensitivity of squamous cell carcinomas is intermediate relative to tumors of other histology [33] Cellular repopulation and hypoxia have been shown to significantly influence radiotherapy outcome in this tumor type

It has been observed from clinical data [46] and confirmed by studies with experimental tumors [23, 35] that the local tumor control probability decreases as the overall treatment time increases with a constant radiation dose, particularly in squamous cell carcinomas This is explained by an increase in the effective net production of tumor cells during the course of radiation treatment To counteract this repopulation of tumor clonogens, the overall treatment time can be reduced by giving the same total radiation dose with multiple fractions per day This strategy is called accelerated radiotherapy There is now evidence from randomized clinical trials that with accelerated radiotherapy, local tumor control can indeed be improved in patients with head and neck and bronchus carcinomas [1, 12, 30, 38]

Tumor cell hypoxia is another well recognized cause for radiation resistance The response of cells to ionizing radiation is strongly dependent upon the availability of oxygen Two types of tumor hypoxia have been described Chronic or diffusion-limited hypoxia occurs at the edge of necrotic areas at a relatively constant distance from blood vessels, the diffusion distance of oxygen in tissue [42] Acute or transient hypoxia results from local and temporary fluctuations in tumor blood perfusion [3] Hypoxia appears to be present in the majority of rodent solid tumors and in xenografted human tumors [26, 34, 43] There is also substantial evidence for hypoxia in human tumors in situ [5] Tumor oxygenation status predicts the prognosis of patients receiving radiotherapy for carcinomas of the uterine cervix and the head and neck [8, 11, 28] A meta-analysis of 72 randomized clinical trials comparing radiotherapy alone or combined with a treatment to modify tumor hypoxia showed improvement of loco-regional control and survival following manipulation of tumor hypoxia [31] When analyzed according to site, this improvement was mainly in head and neck tumors

New approaches in oxygenation modification with radiotherapy aim to simultaneously reduce acute and chronic hypoxia The amide derivative of vitamin B_3, nicotinamide, can reduce the intermittent closure of blood vessels and consequently decrease acute hypoxia [4, 13] Carbogen (95% oxygen and 5% carbon dioxide) breathing can increase the oxygen

partial pressure in tissues and reduce chronic hypoxia in patients with head and neck tumors [24] Many radiosensitizers have shown great promise when used with large single radiation doses, but the benefit has diminished in fractionation studies By contrast, studies in rodent tumors demonstrated significant sensitization when accelerated fractionated radiotherapy was administered together with a combination of carbogen and nicotinamide (ARCON) [35, 36] An enhancement ratio of 1 9 was obtained with doses close to those used clinically, meaning that to obtain the same tumor control rate as with conventional radiotherapy without sensitizers, a 1 9 times lower radiation dose was needed with the ARCON treatment

The aim of this study was to assess the feasibility, toxicity and clinical effectiveness of accelerated radiotherapy with carbogen and nicotinamide as an organ-preserving treatment for carcinoma of the larynx

Patients and methods

Design of the study The toxicity and clinical effectiveness of carbogen and nicotinamide added to a schedule of accelerated radiotherapy was investigated in this study The radiotherapy schedule was tested previously in patients with laryngeal carcinoma and considered tolerable [19] The first 11 patients in this study were treated with the accelerated schedule in combination with carbogen alone When this was shown to be feasible and without unacceptable early toxicity, the next 51 patients were treated with accelerated radiotherapy and both carbogen and nicotinamide

Patients Patients referred to our center from November 1992 with previously untreated stage III and IV carcinoma of the larynx (1992 UICC classification system [16]) were considered for the study Inclusion criteria were an age over 18 years, a WHO performance status of 0-2, no severe heart or lung diseases, no severe liver or kidney function impairments, no severe stridor, no distant metastases and no concurrent treatment for other malignancies Twelve patients were ineligible according to these criteria Five patients were eligible but refused to participate Sixty-two patients were entered between November 1992 and January 1997

The mean age of the patients was 62 years (range 39-83 years) There were 47 men and 15 women All patients had histologically confirmed squamous cell carcinomas Fourteen patients had glottic and 48 patients had supraglottic tumors Diagnostic work-up included examination under anesthesia with biopsy, CT- or MR-scanning and chest X-ray in all patients If an examination under anesthesia had already been performed by the referring

otolaryngologist, this was repeated in our center Ultrasound examination of the neck with fine needle cytology of suspect lymph nodes was performed in 55 of the 62 patients. All patients were discussed in a multi-disciplinary conference for tumor classification and treatment recommendation. Classification of the tumors is given in Table 1. According to the standard institutional protocol, patients with primary tumors classified as T_4 are recommended to undergo laryngectomy Patients with T_4 tumors included in this study either refused surgery or were considered to be poor candidates for laryngectomy

This work was approved by the local ethics committee and written informed consent was obtained from all patients.

Table 1. *TNM-classification of tumors.**

	N_0	N_1	N_{2b}	N_{2c}	Total
T_1	-	-	-	1	1
T_2	-	6	1	3	10
T_3	22	12	2	3	39
T_4	8	1	1	2	12
Total	30	19	4	9	62

*According to UICC 1992 [16]

Radiotherapy Irradiations were given on a linear accelerator and patients were immobilized in custom-made casts. The primary tumor and bilateral neck nodes were irradiated through lateral opposed 4 or 6 MV photon beams. After 30-40 Gy the spinal cord was shielded and the posterior cervical neck nodes were treated with lateral appositional electron beams. The supraclavicular nodes were treated with an anterior photon field The boost dose was delivered through reduced lateral or oblique opposed portals, combined when necessary, with an electron beam to boost nodal areas overlying the spinal cord The initial treatment volume including the primary tumor, metastatic nodes and macroscopically uninvolved nodal areas received 44 Gy Subsequently, a boost of 20 Gy was given to the primary tumor and 24 Gy was given to metastatic nodes to a total dose of 64 and 68 Gy, respectively. The spinal cord dose did not exceed 40 Gy The dose per fraction was 2 Gy and treatments were given daily, five times per week, except during the last week and a half when treatments were given twice daily with an interval between fractions of at least 6 h

The total treatment time was 35-37 days The dose specification was according to Report 29 of the ICRU [15]

Carbogen breathing A scuba-diving breathing regulator (Scubapro, Brussels, Belgium) was used for carbogen delivery This system transports the gas from the reservoir to the patient by way of a two-step pressure reduction The first stage is attached to the reservoir and reduces pressure to 9 atmos (912 kPa) An intermediate pressure hose leads the gas to the second stage which further reduces pressure to 1 atmos (101 kPa) The second stage of the breathing regulator is connected to a disposable anesthetic face mask which is incorporated in the immobilizing cast Details of this breathing system have been described earlier [20] Carbogen breathing commenced 4 min before irradiation and continued throughout

Nicotinamide Nicotinamide (Pharmachemie, Haarlem, The Netherlands) was dissolved in fruit juice and administered orally 1 5 h before irradiations On days when two fractions were given, only one dose of nicotinamide was given before the first treatment Initially the daily dose was 6 g Based on subsequent pharmacokinetic data [14, 18], this was changed to a weight-adjusted dose of 80 mg/kg with a maximum of 6 g from April 1994 and the interval between intake and irradiations was reduced to 1 h from November 1995 Also from November 1995, a dose reduction to 60 mg/kg was introduced for those patients who experienced severe side-effects

Monitoring during treatment and follow-up Assessment of side-effects and tumor response was done weekly during the treatment and thereafter until side-effects started to subside Patients were then seen once every 2 or 3 weeks until healing of skin and mucosa was complete At these visits they were asked if any adverse events had occurred and they were specifically questioned about dysphagia, food intake, nausea and/or vomiting Physical examination included registration of body weight and assessment of mucosal and skin reactions and tumor response Thereafter, evaluations were performed once every 2 months during the first year after treatment, every 3 months in the second year, every 4 months in the third year and every 6 months from the fourth year on Follow-up visits included documentation of any relevant complaints, indirect laryngoscopy and/or laryngoscopy by flexible fiberoptic scope and palpation of the neck When a local recurrence was suspected, examination under anesthesia was performed and suspect abnormalities were biopsied Chest X-rays were done once every 6 months during the first 2 years of

follow-up and once every year thereafter. Thyroid function was monitored before and after treatment.

Statistical analysis Cumulative control and survival rates with standard errors (SE) were calculated from the date of pathologic diagnosis using the Kaplan-Meier method [21] This was done on a Macintosh computer with the Statistica 4 0 software package

Results

Compliance and acute morbidity Ten (16%) of the 62 patients were unable to breathe carbogen during the entire treatment period because of discomfort with the breathing procedure. Eight of these patients were unable to cope with the procedure from the beginning The other two patients discontinued carbogen breathing after 2 and 3 weeks, respectively. Apart from this, carbogen breathing produced no particular side-effects.

Any side-effects that were felt to be related or possibly related to nicotinamide intake are listed in Table 2. The most common side-effects were nausea and vomiting, reported by 69 and 39% of the patients, respectively. Of the 51 patients taking nicotinamide, 17 (33%) discontinued drug intake because of side-effects and nine (18%) had a dose reduction to 60 mg/kg per day, after which they were able to continue nicotinamide intake until the completion of the treatment.

Table 2. *Side-effects attributed to nicotinamide in 51 patients*

Side-effect	No. of patients
nausea	35 (69%)
vomiting	20 (39%)
flushing	2
dizziness	2
epigastric pain	2
gastrointestinal bleeding	1
headache	2
sweating	1
fatigue	1
emotional disturbances	1

All patients completed the treatment within the planned time of 35-37 days All but two patients developed confluent mucositis, i e formation of a confluent fibrinous pseudomembrane The peak incidence was in the 2 weeks following the end of the treatment and the median duration was 6 weeks (range 2-15 weeks) In all cases there was complete healing of the mucosa Due to the mucosal reactions and consequent dysphagia, 17 (27%) patients required temporary feeding by nasogastric tube or percutaneous gastrostomy Indications for tube feeding were a weight loss > 10% of the initial body weight or insufficient intake of liquids The median duration of tube feeding was 7 weeks (range 2-16 weeks) Moist desquamation of the skin was observed in 38 (61%) patients with a median duration of 2 weeks (range 1-12 weeks) and complete healing in all patients

Loco-regional control and survival The median follow-up at the time of analysis was 24 months (range 8-50 months) and no patients have been lost to follow-up Evaluation at 6 weeks after the treatment demonstrated a complete regression of the primary tumor and the nodal metastases in all cases, i e a complete response rate of 100% Five patients experienced a local recurrence at 5, 8, 14, 18, and 31 months, respectively Two of these received carbogen only and the other three received both carbogen and nicotinamide, but of these, two discontinued nicotinamide after 8 and 25 days, respectively, because of side-effects Actuarial local control rates were 92% (SE 3 9%) at 2 years and 87% (SE 6 0%) at 3 years (Fig 1) There was one patient with a neck node recurrence at 13 months The five patients with local recurrence underwent total laryngectomy and the one patient with nodal recurrence underwent a neck dissection and re-irradiation All remained free of loco-regional disease Thus, including salvage surgery, the actuarial loco-regional control was 100% Four patients died of metastatic disease (three cases in the lung and one case in the liver) At the time of analysis all patients alive were free of disease The actuarial overall survival was 85% (SE 5 5%) at 2 years and 77% (SE 7 2%) at 3 years (Fig 2)

Late complications One patient developed laryngeal edema with persistent dysphagia and otalgia 3 months after the completion of treatment, suggestive of radiation-induced chondritis Repeated examinations under anesthesia showed an ulcerating lesion on the epiglottis without histopathologic evidence of recurrent carcinoma This patient underwent a total laryngectomy because of persistent severe pain 9 months after the completion of radiotherapy Histologic examination of the surgical specimen showed chronic inflammation with necrosis and destruction of cartilage, there was no evidence of recurrent carcinoma

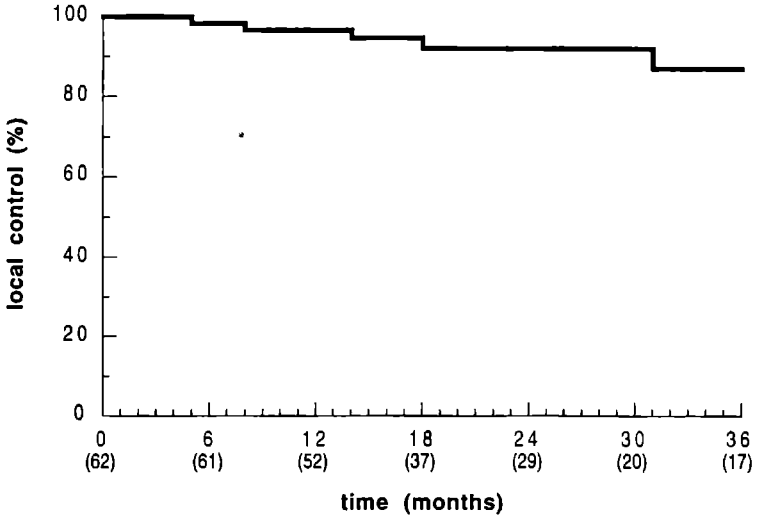


Fig. 1. *Actuarial local tumor control. Numbers in parentheses on abscissa indicate the number of patients at risk.*

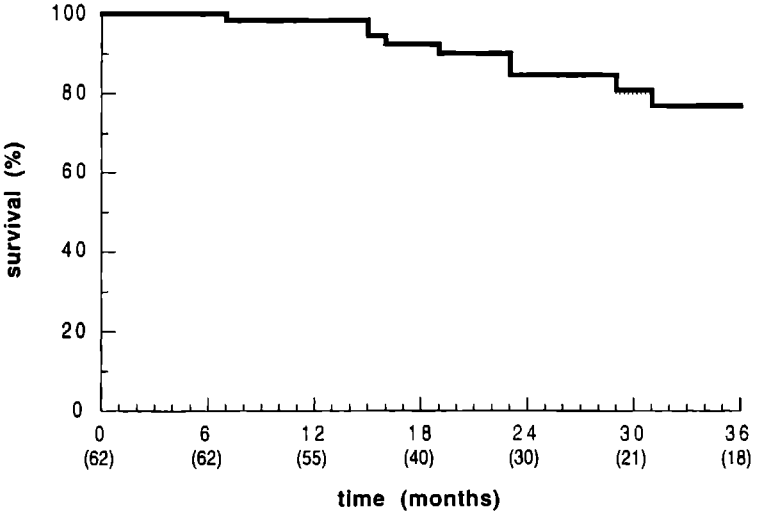


Fig. 2. *Actuarial overall survival. Numbers in parentheses on abscissa indicate the number of patients at risk.*

Three other patients had late episodes of similar symptoms and dysphagia necessitated tube feeding for 2-6 months after which these symptoms settled Temporary or permanent severe laryngeal edema not requiring any surgical intervention was observed in 11 patients One of the six patients who underwent laryngectomy developed a pharyngo-cutaneous fistula postoperatively

Discussion

In many institutions the standard treatment for T_3 and T_4 squamous cell carcinoma of the larynx is still total laryngectomy, with or without postoperative radiotherapy Loco-regional control rates of 68-95% can be obtained with this approach [27, 47] The consequence of total laryngectomy is substantial functional loss, the most important of which is the loss of the natural voice The organ-preserving alternative is radiotherapy However, with conventional methods tumor control is obtained in only about 23-53% of patients depending on site, stage and selection criteria [2, 40, 44] Based on accomplishments of radiobiological research, new approaches in clinical radiotherapy have been developed to improve treatment outcome These include alternative fractionation schedules and methods to improve tumor oxygenation Table 3 summarizes the results of radiotherapy approaches for advanced laryngeal cancer which are further discussed below

Two randomized clinical trials in head and neck cancer, comparing radiotherapy in hyperbaric oxygen and radiotherapy in air, demonstrated a significant improvement of local control with hyperbaric oxygen [9, 10] In the second study, 2-year control rates of 42% with air and 73% with hyperbaric oxygen were obtained for T_3 and T_4 laryngeal carcinomas [9] Delivery of radiation in hyperbaric oxygen is, however, a demanding technique and therefore the approach has not gained general acceptance

The Radiation Therapy Oncology Group (RTOG) conducted a randomized study comparing radiotherapy alone and radiotherapy with carbogen breathing in patients with stage II-IV head and neck carcinomas [37] Overall local tumor control for all head and neck regions combined was 51% with no difference between the two arms A greater control rate was observed in the carbogen arm for the larynx tumors but, due to the small numbers in this subgroup, no significance could be given to this observation This study was criticized because of possible improper timing of carbogen breathing relative to the delivery of radiotherapy In animal studies the maximum sensitizing effect of carbogen was observed after a preirradiation breathing time of 5 min with a decreased effect with longer times,

apparently due to physiological compensatory mechanisms [39] In the RTOG study preirradiation breathing times were generally longer

Nitro-imidazole compounds have been used as hypoxic cell sensitizers in combination with radiotherapy These drugs mimic the sensitizing effect of oxygen In a randomized study, it was demonstrated that radiotherapy with nimorazole (1-(N-β-ethyl-morpholine)-5-nitro-imidazole) improves loco-regional control in stage II-IV supraglottic larynx carcinomas from 35 to 53% [29]

Accelerated radiotherapy for head and neck cancer has been tested in four randomized studies which were recently completed [1, 6, 12, 30] Preliminary results from all four studies are consistent with the hypothesis that shortening of treatment time can improve tumor control The largest gain in loco-regional control (13%) was obtained in the EORTC study [12] However, this was accompanied by an increase of the complication rate requiring further modification of the fractionation schedule

By lowering the dose per fraction and giving multiple fractions per day a higher radiation dose can be delivered to the tumor without increasing late morbidity This hyperfractionation exploits the difference in the fractionation sensitivity between rapidly and slowly renewing tissues to improve tumor control probability Various schedules of hyperfractionation have been tested By reducing the dose per fraction to 1 1-1 2 Gy and delivering two treatments per day the total dose can be escalated to 74-77 Gy This strategy yields a local control rate of 68% for T_3 supraglottic and glottic carcinomas [25, 32] At the MD Anderson Cancer Center, control rates of 77-84% (1 1 and 1 2 Gy per fraction, respectively) were obtained for supraglottic carcinomas [7] In the latter study, about two-thirds of the tumors were T_2 and there were almost no T_4 lesions, thus, overall, disease was less advanced compared to the current study

Wang et al have combined elements of both accelerated and hyperfractionated radiotherapy [45] With a moderate reduction of dose per fraction to 1 6 Gy and total doses of 64-67 Gy given in 6 weeks, they reported a 3-year actuarial control rate of 63% for T_3 and T_4 larynx carcinomas

Another modality that has been investigated for its value in larynx preservation is chemotherapy The Department of Veterans Affairs Cooperative Studies Program coordinated a prospective randomized study in patients with stage III-IV laryngeal carcinoma [41] This trial compared a standard treatment of surgical resection followed by radiotherapy and an experimental treatment in which neoadjuvant chemotherapy (cisplatin and 5-fluorouracil) was followed by radiotherapy for responders and surgery for non-responders The distribution of patients by T-stage was very similar to the current study For the 166 patients assigned to the chemotherapy arm, the rate of larynx preservation after

Table 3. *Radiotherapy for advanced laryngeal carcinoma, literature overview.*

First author	Tumor site	T-stage	No. of patients	Treatment	Tumor control rate (%)	Remarks
Barton [2]	glottic	T_3	146	conventional radiotherapy	47	actuarial local relapse-free at 5 years
		T_4	84		41	
	supraglottic	T_3	45		51	
		T_4	202		50	
Terhaard [40]	larynx	T_3	104	conventional radiotherapy	53	actuarial local control at 3 years
Wang [44]	glottic	T_3	70	conventional radiotherapy	36	actuarial local control at 3 years
	supraglottic	T_3	87		37	no evidence of disease actuarial
		T_4	131		23	rate at 5 years
Henk [9]	larynx	T_{3-4}	25	conventional radiotherapy	42	actuarial local control at 2 years
			24	hypofractionated radiotherapy in hyperbaric oxygen	73	
Rubin [37]	larynx	T_{2-4}	20	conventional radiotherapy	60	actuarial local control at 2 years
			24	conventional radiotherapy with carbogen	70	
Overgaard [29]	supraglottic	T_{1-4}	57	conventional radiotherapy	35	actuarial loco-regional control at 5 years
		(stage II-IV)	68	conventional radiotherapy with nimorazole	53	
Mendenhall [25]	supraglottic	T_3	60	hyperfractionated radiotherapy	68	local control at 5 years (product-limit method)

Table 3. *Radiotherapy for advanced laryngeal carcinoma, literature overview (continued)*

First author	Tumor site	T-stage	No. of patients	Treatment	Tumor control rate (%)	Remarks
Parsons [32]	glottic	T_3	28	hyperfractionated radiotherapy	68	local control with minimal 2-year follow-up
Garden [7]	supraglottic	mainly T_{2-3}	102	hyperfractionated radiotherapy	77-84	actuarial local control at 2 years
Wang [45]	larynx	T_{3-4}	73	hyperfractionated/accelerated radiotherapy	63	actuarial local control at 3 years
Veterans Affairs [41]	larynx	T_{1-4} (stage III-IV)	166	surgery and conventional radiotherapy	-	
			166	chemotherapy and conventional radiotherapy (surgery for poor responders)	66	larynx preservation at 2 years
Keane [22]	larynx	T_{1-4} (stage III-IV)	65	conventional radiotherapy	45	actuarial local relapse-free at 2 years, no difference between groups
			64	split-course radiotherapy and concomitant chemotherapy	45	
Current study	larynx	T_{1-4} (stage III-IV)	62	ARCON	92	actuarial local control at 2 years

2 years was 66% Another phase III trial compared continuous course radiotherapy with split course radiotherapy plus concurrent chemotherapy (mitomycin C and 5-fluorouracil) for advanced laryngeal and hypopharyngeal carcinoma [22] The actuarial 2-year local relapse free rate for the larynx carcinomas was 45% in both arms (N = 129)

In the current study we combined accelerated radiotherapy with carbogen to reduce chronic diffusion-limited tumor hypoxia and with nicotinamide to reduce acute hypoxia Carbogen was preferred over pure oxygen because of the respiratory stimulation and a possible advantageous effect on microregional blood flow This approach yields a 2-year local control rate of 92% for patients with stage III-IV laryngeal carcinoma This is higher than any previous report in the literature for this category of patients

The compliance rate for carbogen breathing was 84% The most important side-effects of nicotinamide were nausea and vomiting which caused 33% of patients to discontinue drug intake This moderate compliance to nicotinamide calls for measures to improve drug tolerance Anti-emetic treatment can be intensified and the drug dose can possibly be reduced without losing the sensitizing effect Nicotinamide tolerance and pharmacokinetics have been discussed in detail in previous papers [17, 18] Studies in rodent tumors demonstrated a significant improvement of the sensitizing effect of the combination of carbogen and nicotinamide relative to carbogen alone [35, 36] Of the five patients in this study who developed a local recurrence, two were in the group without nicotinamide and two discontinued nicotinamide intake because of side-effects This study, however, was not designed to assess the relative effectiveness of each of the individual components of ARCON A large-scale clinical study would be needed to address this question

Accelerated radiotherapy elevates radiation reactions not only in tumors but also in rapidly repopulating normal tissues, in particular the mucosal lining [19] There is some additional enhancement from carbogen and nicotinamide [17] With the schedule used in this study, almost all patients developed confluent mucositis and 27% required temporary tube feeding However, there was complete healing of the mucosa in all patients and we consider these side-effects as acceptable

One of our patients developed necrosis of the laryngeal cartilage requiring laryngectomy The initial study with hyperbaric oxygen by Henk et al demonstrated a decrease in radiation tolerance of the laryngeal cartilage [10] A 10% reduction of the total radiation dose in the subsequent study reduced the laryngeal complications to a level seen with treatment in air [9] Since a similar effect might have been expected from normobaric carbogen with nicotinamide in the current study, we limited the total dose to the larynx to 64 Gy which is almost a 10% reduction relative to our conventional dose of 70 Gy The good results despite this reduced radiation dose strongly support the concept of an increased

tumor effectiveness of these biologically-based treatment modifications. A phase III trial is needed to assess the magnitude of the therapeutic gain.

These preliminary results indicate that in advanced laryngeal cancer, high tumor control rates can be obtained when accelerated radiotherapy is combined with carbogen and nicotinamide. This approach offers excellent possibilities for larynx preservation.

Acknowledgements

The authors thank K. Kian Ang, J. Denekamp, S. Dische and M.I. Saunders for their critical review of the manuscript.

References

1. Ang, K.K., Trotti, A., Garden, A.S., et al. Overall time factor in postoperative radiation: results of a prospective randomized trial. Radiother. Oncol. 40 (Suppl 1): S30, 1996.

2. Barton, M.B., Keane, T.J., Gadalla, T. and Maki, E. The effect of treatment time and treatment interruption on tumour control following radical radiotherapy of laryngeal cancer. Radiother. Oncol. 23: 137-143, 1992.

3. Brown, J.M. Evidence for acute hypoxic cells in mouse tumours and a possible mechanism of reoxygenation. Br. J. Radiol. 52: 650-656, 1979.

4. Chaplin, D.J., Horsman, M.R. and Trotter, M.J. The effect of nicotinamide on the microregional heterogeneity of oxygen delivery within a murine tumour. J. Natl. Cancer Inst. 82: 672-676, 1990.

5. Chapman, J.D. Measurement of tumor hypoxia by invasive and non-invasive procedures: a review of recent clinical studies. Radiother. Oncol. 20 (Suppl): 13-19, 1991.

6. Dische, S., Saunders, M.I., Barrett, A., Harvey, A., Gibson, D. and Parmar, M.K.B. A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother. Oncol. 44: 123-136, 1997.

7. Garden, A.S., Morrison, W.H., Ang, K.K. and Peters, L.J. Hyperfractionated radiation in the treatment of squamous cell carcinomas of the head and neck: a comparison of two fractionation schedules. Int. J. Radiat. Oncol. Biol. Phys. 31: 493-502, 1995.

8. Gatenby, R.A., Kessler, H.B., Rosenblum, J.S., et al. Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 14: 831-838, 1988.

9. Henk, J.M. Late results of a trial of hyperbaric oxygen and radiotherapy in head and neck cancer: a rationale for hypoxic cell sensitizers? Int. J. Radiat. Oncol. Biol. Phys. 12: 1339-1341, 1986.

10. Henk, J.M., Kunkler, P.B. and Smith, C.W. Radiotherapy and hyperbaric oxygen in head and neck cancer. Lancet ii: 101-103, 1977.

11. Hockel, M., Schlenger, K., Mitze, M., Schäffer, U. and Vaupel, P. Hypoxia and radiation response in human tumors. Sem. Radiat. Oncol. 6 3-9, 1996.

12. Horiot, J C., Bontemps, P , van den Bogaert, W., et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial Radiother. Oncol 44· 111-121, 1997.

13 Horsman, M R., Chaplin, D.J. and Overgaard, J. Combination of nicotinamide and hyperthermia to eliminate radioresistant chronically and acutely hypoxic tumour cells. Cancer Res. 50 7430-7436, 1990

14. Hoskin, P J , Stratford, M R L., Saunders, M I., Hall, D.W , Dennis, M F. and Rojas, A Administration of nicotinamide during CHART: pharmacokinetics, dose escalation, and clinical toxicity. Int J. Radiat. Oncol. Biol. Phys. 32: 1111-1119, 1995

15. International Commission on Radiation Units and measurements: Dose specification for reporting external beam therapy with photons and electrons. Report 29. ICRU Publications, Washington, DC, 1978.

16 International Union Against Cancer: TNM classification of malignant tumours. 4th edition Springer-Verlag, Berlin, 1992

17. Kaanders, J.H.A.M , Pop, L.A.M , Marres, H A M., van der Maazen, R.W M., van der Kogel, A J and van Daal, W.A J Radiotherapy with carbogen breathing and nicotinamide in head and neck cancer: feasibility and toxicity. Radiother. Oncol. 37: 190-198, 1995

18 Kaanders, J H A M., Stratford, M R.L., Liefers, J , et al. Administration of nicotinamide during a five- to seven-week course of radiotherapy: pharmacokinetics, tolerance, and compliance Radiother Oncol 43. 67-73, 1997.

19. Kaanders, J H A M., van Daal, W.A J., Hoogenraad, W J. and van der Kogel, A J. Accelerated fractionation radiotherapy for laryngeal cancer, acute and late toxicity. Int. J Radiat. Oncol. Biol Phys 24: 497-503, 1992.

20. Kaanders, J H A M and van der Maazen, R W.M. A convenient and reliable method for carbogen breathing in man. Radiother. Oncol. 29: 341-343, 1993.

21. Kaplan, E.L. and Meier, P. Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc. 53: 457-481, 1958.

22. Keane, T.J., Cummings, B.J., O'Sullivan, B., et al. A randomized trial of radiation therapy compared to split course radiation therapy combined with mitomycin C and 5-fluorouracil as initial treatment for advanced laryngeal and hypopharyngeal squamous carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 25: 613-618, 1993.

23. Kummermehr, J., Dörr, W. and Trott, K.R. Kinetics of accelerated repopulation in normal and malignant squamous epithelia during fractionated radiotherapy. Br. J. Radiol. 24 (Suppl): 193-199, 1992.

24. Martin, L., Lartigau, E., Weeger, P., et al. Changes in the oxygenation of head and neck tumors during carbogen breathing. Radiother. Oncol. 27: 123-130, 1993.

25. Mendenhall, W.M., Parsons, J.T., Mancuso, A.A., Stringer, S.P. and Cassisi, N.J. Radiotherapy for squamous cell carcinoma of the supraglottic larynx: an alternative to surgery. Head Neck 18: 24-35, 1996.

26. Moulder, J.E. and Rockwell, S. Hypoxic fractions of solid tumors: experimental techniques, methods of analysis, and a survey of existing data. Int. J. Radiat. Oncol. Biol. Phys. 10: 695-712, 1984.

27. Nguyen, T.D., Malissard, L., Théobald, S., et al. Advanced carcinoma of the larynx: results of surgery and radiotherapy without induction chemotherapy (1980-1985): a multivariate analysis. Int. J. Radiat. Oncol. Biol. Phys. 36: 1013-1018, 1996.

28. Nordsmark, M., Overgaard, M. and Overgaard, J. Pretreatment oxygenation predicts radiation response in advanced squamous cell carcinoma of the head and neck. Radiother. Oncol. 41: 31-39, 1996.

29. Overgaard, J., Sand Hansen, H., Overgaard, M., et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) protocol 5-85. Radiother. Oncol. 46: 135-146, 1998.

30. Overgaard, J., Sand Hansen, H., Overgaard, M., et al. Conventional radiotherapy as primary treatment of squamous cell carcinoma of the head and neck. A randomized multicenter study of 5 versus 6 fractions per week - report from the DAHANCA 7 trial. Int. J. Radiat. Oncol. Biol. Phys. 39 (Suppl): 188, 1997.

31. Overgaard, J. Importance of tumor hypoxia in radiotherapy. A meta-analysis of controlled clinical trials. Radiother. Oncol. 24 (Suppl): S64, 1992.

32. Parsons, J.T., Mendenhall, W.M., Stringer, S.P., Cassisi, N.J. and Million, R.R. Twice-a-day radiotherapy for squamous cell carcinoma of the head and neck: the University of Florida experience. Head Neck 15: 87-96, 1993.

33. Peters, L.J. Inherent radiosensitivity of tumor and normal tissue cells as a predictor of human tumor response. Radiother. Oncol. 17: 177-190, 1990.

34. Rockwell, S. and Moulder, J.E. Hypoxic fractions of human tumors xenografted into mice: a review. Int. J. Radiat. Oncol. Biol. Phys. 19: 197-202, 1990.

35. Rojas, A., Hirst, V.K., Calvert, A.S. and Johns, H. Carbogen and nicotinamide as radiosensitizers in a murine mammary carcinoma using conventional and accelerated radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 34: 357-365, 1996.

36. Rojas, A. Radiosensitization with normobaric oxygen and carbogen. Radiother. Oncol. 20 (Suppl 1): 65-70, 1991.

37. Rubin, P., Hanley, J., Keys, H.M., Marcial, V. and Brady, L. Carbogen breathing during radiation therapy. The Radiation Therapy Oncology Group Study. Int. J. Radiat. Oncol. Biol. Phys. 5: 1963-1970, 1979.

38. Saunders, M.I., Dische, S., Barrett, A., Harvey, A., Gibson, D. and Parmar, M.K.B. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. Lancet 350: 161-165, 1997.

39. Siemann, D.W., Hill, R.P. and Bush, R.S. The importance of the pre-irradiation breathing times of O_2 and carbogen (5% CO_2: 95% O_2) on the in vivo radiation response of a murine sarcoma. Int. J. Radiat. Oncol. Biol. Phys. 2: 903-911, 1977.

40. Terhaard, C.H.J., Karim, A.B.M.F., Hoogenraad, W.J., et al. Local control in T_3 laryngeal cancer treated with radical radiotherapy, time dose relationship: the concept of nominal standard dose and linear quadratic model. Int. J. Radiat. Oncol. Biol. Phys. 20: 1207-1214, 1991.

41. The Department of Veterans Affairs Laryngeal Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N. Engl. J. Med. 324: 1685-1690, 1991.

42. Thomlinson, R.H. and Gray, L.H. The histological structure of some human lung cancers and the possible implications for radiotherapy. Br. J. Cancer 9: 539-549, 1955.

43. Vaupel, P., Okunieff, P., Kallinowski, F. and Neuringer, L.J. Correlations between ^{31}P-NMR spectroscopy and tissue O_2 tension measurement in a murine fibrosarcoma. Radiat. Res. 120: 477-493, 1989.

44. Wang, C.C. Radiation therapy of laryngeal tumors: curative radiation therapy. In: Comprehensive management of head and neck tumors. Vol 1, pp 906-918. Editors: Thawley, S.E., Panje, W.R., Batsakis, J.G. and Lindberg, R.D. WB Saunders, Philadelphia, PA, 1987.

45. Wang, C.C., Blitzer, P.H. and Suit, H.D. Twice-a-day radiation therapy for cancer of the head and neck. Cancer 55: 2100-2104, 1985.

46. Withers, H.R., Taylor, J.M.G. and Maciejewski, B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol. 27: 131-146, 1988.

47. Yuen, A., Medina, J.E., Goepfert, H. and Fletcher, G. Management of stage T_3 and T_4 glottic carcinomas. Am. J. Surg. 184: 467-472, 1984.

CHAPTER 8

SUMMARY / SAMENVATTING

Summary

Chapter 1 is an introduction and briefly reviews the most important mechanisms of radiation resistance. The focus is on squamous cell carcinomas of the head and neck. Radiotherapy is a principal treatment modality for this category of malignancies and of special interest because of its organ preserving potential. Of particular importance in head and neck carcinomas are cellular repopulation and hypoxia. This has been demonstrated in experimental and human tumors. Novel approaches in radiotherapy have been developed to overcome these resistance mechanisms. Several were tested in randomized trials and proved to be effective. Notwithstanding the successfulness of some of these new treatment approaches, there is room for further improvement. It is suggested that further work should concentrate on two strategies: 1) Identification of tumors or classes of tumors that are most suitable for either of the new treatments and 2) Simultaneously counteracting different radioresistance mechanisms by combination of treatment modifications. The latter was the aim of this work and it is outlined how accelerated radiotherapy together with methods for hypoxic modification was introduced in the clinic. This treatment is called "**ARCON**: **A**ccelerated **R**adiotherapy with **C**arb**O**gen and **N**icotinamide".

Chapter 2 is a study on the acute and late toxicity of a newly developed schedule for accelerated radiotherapy. A moderate reduction of overall treatment time to 5-5.5 weeks was accomplished by giving two radiation fractions a day during the last part of the treatment. The total dose and dose per fraction were unchanged relative to conventional treatment. The feasibility and toxicity of this schedule were assessed in patients with laryngeal cancer. Early mucosal reactions and, to a lesser extent, also skin reactions were enhanced compared to conventional treatment. There was an indication of a small increase in the incidence of late effects, i.e. laryngeal edema, as well. It is concluded that the toxicity of this schedule remains within the limits of tolerance. Further shortening of overall treatment time without reduction of total dose is not recommended because this might lead to unacceptable acute mucosal reactions.

The experimental and clinical data on radiation mucositis are reviewed in **chapter 3** with the aim to assess whether indeed the upper aerodigestive tract mucosa is limiting to treatment intensification by altered fractionation. It is concluded that the maximum achievable gain in treatment time is 2 weeks, relative to a conventional treatment of 7 weeks, with the mucosa being the limiting tissue. Any further acceleration requires a reduction of dose. This can be disadvantageous, in particular for tumors with relatively low intrinsic

radiosensitivity It is also concluded that manipulations with the temporal distribution of dose and fraction dose, and optimization of intervals between fractions may improve tolerance but are unlikely to allow a significant further intensification of the existing accelerated schedules Dose escalation by hyperfractionation seems to be limited by late sequelae more than by acute mucosal reactions Finally, it is briefly discussed which agents are available to prevent or ameliorate radiation mucositis Unfortunately, none of these agents appears to be sufficiently effective to recommend its application as standard practice

The effect of carbogen (95% O_2 + 5% CO_2) breathing, one of the components of ARCON, is a rise of the oxygen partial pressure in the blood and tissues and a consequent reduction of diffusion-limited hypoxia in tumors Patients with head and neck tumors may have difficulties with gas breathing, in particular when the tumor is located in the upper airway In addition, for these patients a custom-made cast is needed for immobilization during irradiations **Chapter 4** describes a breathing system that was developed to be combined with the fixating cast and which would ensure good compliance This system is based on professional diving equipment and a disposable anesthetic face mask which is incorporated in the fixating cast There was full compliance with this method of carbogen breathing in 84% of 62 patients with laryngeal cancer (chapter 7)

Chapter 5 reports on the feasibility and toxicity of radiotherapy to the head and neck area when combined with carbogen and nicotinamide Nicotinamide, the third component of ARCON can modify transient hypoxia by opening temporarily closed tumor blood vessels, thereby increasing blood perfusion Carbogen and nicotinamide were added in consecutive steps to schedules of conventional and accelerated radiotherapy Thirty-four patients with far advanced tumors of the oral cavity and oropharynx received conventional radiotherapy with carbogen (N = 16) or with carbogen and nicotinamide (N = 18) Forty patients with laryngeal and hypopharyngeal carcinomas were treated with accelerated radiotherapy combined with carbogen (N = 16) or with carbogen and nicotinamide (N = 24) Some enhancement of skin reactions was observed with nicotinamide but generally the skin healed rapidly and the reactions were well within the limits of tolerance With the accelerated schedule alone almost all patients developed confluent mucositis (chapter 2) Additional enhancement by carbogen and nicotinamide was expressed as delayed healing of the mucosal lining This toxicity was manageable and within acceptable limits A further intensification of the treatment is however not advocated because this might then lead to non-healing mucosal damage in some patients Frequent side-effects of nicotinamide were nausea (60%) and vomiting (36%) Severe renal dysfunction was associated with

nicotinamide intake in three patients It is recommended that nicotinamide should not be given concomitantly with nephrotoxic medication or to patients with impaired renal function

The pharmacokinetics, tolerance, and compliance to nicotinamide were further investigated in **chapter 6** In 40 patients nicotinamide plasma levels were determined A full pharmacokinetic profile was obtained on the first day of the treatment followed by daily samples at the time of irradiation during the first and last weeks In all patients peak concentrations adequate for radiosensitization could be obtained The plasma levels decreased however towards the end of the treatment which was partly attributed to reduced compliance There appeared to be an association between severe side-effects and high plasma concentrations over subsequent days There was an indication that tolerance could be improved by a 25% reduction of the drug dose Whether adequate plasma levels can be obtained with this reduced dose is the subject of ongoing investigations

In **chapter 7** the effectiveness of ARCON in terms of tumor response was assessed in 62 patients with stage III-IV laryngeal carcinomas Accelerated radiotherapy was given with carbogen in the initial 11 patients and with both carbogen and nicotinamide in the subsequent 51 patients With a median follow-up of 24 months, the actuarial local control rate at 2 years was 92% There was one regional recurrence Including salvage surgery the ultimate loco-regional control rate was 100% The actuarial overall survival rate was 85% at 2 years One patient underwent laryngectomy for radiation-induced cartilage necrosis The literature on radiotherapy for advanced laryngeal cancer is briefly reviewed Control rates with conventional methods are in the range of 23-53% This can be improved by hyperfractionation and use of hypoxic modifiers to 53-84% depending on site, stage, and selection criteria The control rate in the current study is higher than any previous report in the literature and must be confirmed, preferably in a phase III trial The organ preserving potential of ARCON can offer a significant improvement of the quality of life of patients with advanced laryngeal cancer

Samenvatting

Hoofdstuk 1 is een introductie en geeft een beknopt overzicht van de belangrijkste mechanismen die de stralingsgevoeligheid van een tumor bepalen Het accent ligt hierbij op de plaveiselcelcarcinomen van het hoofd-, halsgebied Radiotherapie is een van de belangrijkste behandelingsmodaliteiten voor deze categorie van maligniteiten en met name interessant vanwege het orgaansparende karakter Bij carcinomen van het hoofd-, halsgebied spelen met name tumorcel repopulatie en hypoxie een belangrijke rol Dit is aangetoond in zowel experimentele als humane tumoren Nieuwe benaderingen in de radiotherapie zijn er op gericht om deze resistentie mechanismen zoveel mogelijk te compenseren De effectiviteit van enkele van dergelijke nieuwe behandelingen is bewezen in gerandomiseerde studies Desalniettemin is er ruimte voor verdere verbeteringen Het voorstel is daarom om verder onderzoek te concentreren op een tweetal strategieen 1) Identificatie van tumoren of categorieen van tumoren die het meest geschikt zijn voor de diverse nieuwe behandelingen en 2) Gebruik maken van een combinatie van verschillende modificaties van de behandeling om zodoende te compenseren voor meerdere resistentie mechanismen tegelijk Dit laatste was het doel van dit onderzoek In dit proefschrift wordt beschreven hoe versneld gefractioneerde bestraling tezamen met methoden voor modificatie van hypoxie voor klinische toepassing werd geintroduceerd Deze behandeling wordt "**ARCON**" genoemd "**A**ccelerated **R**adiotherapy with **C**arb**O**gen and **N**icotinamide"

Hoofdstuk 2 beschrijft een studie naar de acute en late toxiciteit van een nieuw ontwikkeld schema voor versneld gefractioneerde bestraling Door gedurende het laatste deel van de behandeling twee bestralingen per dag te geven werd de totale behandelingsduur verkort tot 5-5,5 weken De totale dosis en dosis per fractie bleven onveranderd in vergelijking met het conventionele schema De uitvoerbaarheid en toxiciteit van dit schema werden onderzocht bij patienten met een larynxcarcinoom De acute slijmvliesreacties en, in mindere mate, ook de huidreacties waren toegenomen in vergelijking met conventionele behandeling Er waren tevens aanwijzingen voor een geringe toename van de incidentie van late effecten, namelijk oedeem van de larynx De conclusie van deze studie is dat het betreffende schema voor versnelde fractionering tolerabel is Nog verdere verkorting van de behandelingsduur zonder reductie van de bestralingsdosis wordt echter afgeraden omdat dit mogelijk kan leiden tot onacceptabele acute toxiciteit van het slijmvlies

Een overzicht van de experimentele en klinische gegevens betreffende bestralingsmucositis wordt gegeven in **hoofdstuk 3** Doel hiervan is om te onderzoeken of

inderdaad de reactie van het slijmvlies van de mond- en keelholte beperkend is bij verdere intensivering van fractioneringsschema's Geconcludeerd wordt dat ten opzichte van een conventioneel schema van 7 weken de behandelingsduur met maximaal 2 weken verkort kan worden waarbij de slijmvliestoxiciteit de beperkende factor wordt. Wil men de behandelingsduur nog verder verkorten dan is ook een reductie van de totale bestralingsdosis nodig Dit kan nadelig zijn, met name bij tumoren met een relatief lage intrinsieke stralingsgevoeligheid Uit de gegevens wordt ook geconcludeerd dat de tolerantie wellicht verbeterd kan worden door optimalisatie van de verdeling van dosis in de tijd, van de dosis per fractie en van de tijdsintervallen tussen de fracties De verwachting is echter niet dat hierdoor een significante verdere verkorting van de behandelingsduur mogelijk wordt Verhogen van de dosis door hyperfractionering lijkt meer beperkt te worden door de late effecten van bestraling dan door de acute slijmvliesreacties Besloten wordt met een korte bespreking van potentiele middelen die bestralingsmucositis kunnen voorkomen of verminderen Helaas blijkt geen van deze middelen effectief genoeg om routinematige toepassing in de dagelijkse praktijk aan te bevelen

Het ademen van carbogeen (95% O_2 + 5% CO_2), een van de componenten van ARCON, veroorzaakt een toename van de zuurstofspanning in bloed en weefsels en daarmee een afname van de zogenaamde "diffusie afhankelijke" hypoxie in tumoren Patienten met hoofd-, halstumoren kunnen moeite hebben met het ademen van het carbogeengas, met name wanneer de tumor in de bovenste luchtweg is gelokaliseerd Daarnaast wordt voor immobilisatie tijdens de bestralingen gebruik gemaakt van een individueel op maat gemaakt gezichtsmasker **Hoofdstuk 4** beschrijft een ademsysteem dat gecombineerd kan worden met het gezichtsmasker en dat tevens goed verdragen wordt en voldoende therapietrouw verzekert Dit systeem is gebaseerd op professionele duikapparatuur en een anesthesiekapje dat in het gezichtsmasker wordt gebouwd Het carbogeen ademen verliep geheel adequaat bij 84% van 62 patienten met een larynxcarcinoom (hoofdstuk 7)

Hoofdstuk 5 beschrijft een studie naar de uitvoerbaarheid en de toxiciteit van radiotherapie in het hoofd-, halsgebied wanneer dit gecombineerd wordt met carbogeen en nicotinamide Nicotinamide, de derde component van ARCON, kan de zogenaamde "tijdelijke" hypoxie doen verminderen door het heropenen van bloedvaten die tijdelijk gesloten zijn waardoor de bloeddoorstroming in de tumor verbetert Carbogeen en nicotinamide werden stapsgewijs toegevoegd aan zowel conventionele als versneld gefractioneerde bestraling Vierendertig patienten met een ver gevorderde tumor van de

mondholte of orofarynx werden behandeld met conventionele radiotherapie gecombineerd met carbogeen (N = 16) of met carbogeen én nicotinamide (N = 18) Veertig patienten met larynx- of hypofarynxcarcinomen werden behandeld met versnelde fractionering in combinatie met carbogeen (N = 16) of met carbogeen én nicotinamide (N = 24) Er was enige toename van de huidreactie met nicotinamide maar in het algemeen herstelde de huid snel en deze bijwerking werd goed verdragen Met het versnelde schema ontwikkelden vrijwel alle patienten een confluente mucositis (hoofdstuk 2) Er was een verdere toename van de slijmvliesreactie door toevoeging van carbogeen en nicotinamide, hetgeen tot uiting kwam als een vertraagde genezing van het slijmvlies Deze bijwerking bleef binnen hanteerbare en acceptabele grenzen Een verdere intensivering van de behandeling wordt echter ontraden omdat dit dan wellicht kan leiden tot irreversibele schade van het slijmvlies bij een deel van de patienten De meest voorkomende bijwerkingen van nicotinamide waren misselijkheid (60%) en braken (36%) Bij drie patienten was er sprake van een ernstige nierinsufficientie onder nicotinamide gebruik Aanbevolen wordt om nicotinamide niet gelijktijdig te geven met andere, nefrotoxische, medicatie en ook niet aan patienten met een gecompromitteerde nierfunctie

De farmacokinetische eigenschappen alsmede de tolerantie en de compliantie voor nicotinamide werden verder onderzocht in **hoofdstuk 6** Bij 40 patienten werd de concentratie van nicotinamide in het plasma bepaald Op de eerste dag van bestraling werd een volledig profiel van de plasmaconcentraties verkregen, gevolgd door dagelijkse bepalingen op het moment van bestraling tijdens de eerste en laatste week van de behandeling Bij alle patienten konden maximale plasmaconcentraties bereikt worden die voldoende hoog waren om een sensibiliserend effect te verkrijgen De plasmaconcentraties werden echter lager naarmate de bestralingsbehandeling vorderde Gedeeltelijk werd dit toegeschreven aan een afname van de therapietrouw Er bleek een correlatie te bestaan tussen het optreden van ernstige bijwerkingen en hoge plasmaconcentraties op opeenvolgende dagen Er was een aanwijzing dat de tolerantie mogelijk verbeterd kan worden door een dosisreductie van 25% Of met deze gereduceerde dosis ook adequate plasmaconcentraties kunnen worden verkregen is thans onderwerp van onderzoek

Hoofdstuk 7 beschrijft een onderzoek naar het tumor-effect van ARCON bij 62 patienten met een stadium III of IV larynxcarcinoom Versneld gefractioneerde bestraling werd gegeven in combinatie met carbogeen bij de eerste 11 patienten en in combinatie met zowel carbogeen als nicotinamide bij de volgende 51 patienten De actuariele lokale controle na 2 jaar was 92% bij een mediane follow-up van 24 maanden Er was één patient met een

regionaal recidief De uiteindelijke loco-regionale controle na "salvage"-chirurgie was 100% De actuariele overleving na 2 jaar was 85% Eén patient onderging een laryngectomie vanwege een door de bestraling geinduceerde kraakbeennecrose In dit hoofdstuk wordt verder een beknopt overzicht gegeven van de resultaten van radiotherapie bij het gevorderde larynxcarcinoom Met conventionele methoden kan bij 23-53% van de patienten tumor-controle worden verkregen Met hyperfractionering en methoden voor modificatie van hypoxie kan dit worden verbeterd tot 53-84% afhankelijk van lokalisatie en stadium van de tumor alsmede toegepaste selectiecriteria De lokale controle die in deze studie werd bereikt is hoger dan bij enig eerder gepubliceerd onderzoek Dit resultaat dient te worden bevestigd, bij voorkeur middels een gerandomiseerde fase III studie Het orgaansparend potentieel van ARCON kan een belangrijke verbetering van de kwaliteit van leven opleveren bij patienten met een gevorderd larynxcarcinoom

DANKWOORD / ACKNOWLEDGEMENTS

Velen hebben hun bijdrage geleverd aan dit proefschrift. Graag wil ik ieder hiervoor hartelijk bedanken. Sommigen wil ik graag apart noemen.

Prof. A.J. van der Kogel. Bert, jij bent de "wetenschappelijke motor" van ons instituut. Het feit dat je mijn promotor bent bewijst overduidelijk dat je met succes de brug tussen laboratorium en kliniek hebt geslagen. Bedankt voor je altijd enthousiaste begeleiding.

Prof. W.A.J. van Daal. Willem, jij hebt het instituut gevormd tot wat het nu is. Je "terughoudend leiderschap" heb ik als plezierig en leerzaam ervaren. Op belangrijke momenten was jouw faciliterende invloed doorslaggevend voor het welslagen van dit onderzoek.

Prof. K.K. Ang. Kian, my year in Houston was a very valuable one. Thanks for sharing your expertise in head and neck radiotherapy and for showing me the advantages of being well-organized. It was a great time.

Luc Pop. Luc, de patiënten uit dit onderzoek hebben jij en ik samen behandeld. Jij hebt me laten zien wat "zorg voor de patiënt" is. Bedankt voor de plezierige samenwerking collega.

Richard van der Maazen. Richard, als chef de policlinique waak jij ervoor dat we niet "verdrinken" in de patiëntenzorg en dat er tijd overschiet voor de wetenschap. Niet zelden is dit een ondankbare taak. Te meer een reden om hier mijn waardering uit te spreken.

Jan Bussink. Jan, de afbeelding op de omslag van dit proefschrift is een product van onze samenwerking en symboliseert onze onderzoekslijn. Ik verheug me op de voortzetting van deze prettige samenwerking.

Leden van de Nijmeegse Hoofd-, Hals Werkgroep. Beste vrienden, zonder jullie medewerking was dit onderzoek niet mogelijk geweest. Ik ben er trots op lid te zijn van deze werkgroep die functioneert op basis van wederzijds respect.

Janine Liefers. Janine, bedankt voor de begeleiding van de patienten en het datamanagement. Je hebt me veel werk uit handen genomen.

Alle medewerkers van het Instituut voor Radiotherapie. Vrijwel iedereen heeft op de een of andere wijze wel bijgedragen aan "de ARCON studie". Allen bedankt voor de enthousiaste inzet en voor de belangstelling.

Pap en mam, bedankt voor wat ik van jullie heb meegekregen. De basis voor dit proefschrift ligt bij jullie.

María José, je hebt je geen ogenblik om dit proefschrift bekommerd maar des te meer om Paula en om mij Je bent een geweldige moeder en echtgenote.

Paula, bij thuiskomst van het werk vraag jij me wel eens: "En pap, hoeveel patienten heb je vandaag beter gemaakt?".. .. Bedankt voor je spontane en vooral relativerende belangstelling schat.

CURRICULUM VITAE

Johannes H A M Kaanders was born on May 10th, 1959, in Vught, The Netherlands He graduated from High School (Gymnasium β, Maurick College in Vught) in 1977 That year he went to Rotterdam to study medicine (1977-1984) at the Erasmus University In 1984 he moved to Nijmegen and worked as a resident at the Institute of Radiotherapy, University Hospital Nijmegen He started his training in radiation oncology at the same institute in 1986 (Prof Willem A J. van Daal) In 1989 he graduated for his ECFMG-exam and continued his training with a one-year fellowship (Anna Hamann fellowship, 1989-1990) at the Department of Radiotherapy of the University of Texas M D Anderson Cancer Center, Houston, USA (Prof Lester J Peters & Prof K Kian Ang) During this year he subspecialized in head and neck radiotherapy In 1990 he qualified and registered as a radiation oncologist Since 1990 he is a member of the staff of the Institute of Radiotherapy at the University Hospital Nijmegen He is married with María José Peiró and they have a daughter named Paula.

LIST OF PUBLICATIONS

Papers

De Filippi, J.P., Kaanders, J.H.A.M. and Hofman, A. Sodium in diet and milk of breastfeeding women. Acta Paediatr. Scand. 70: 417-418, 1981.

Kaanders, J.H.A.M. and Rutten, E.H.J.M. De incidentie van neuro-ectodermale hersentumoren (dutch). Kanker 11: 130-132, 1987.

Van Diejen, D., Driessen, J.J. and Kaanders, J.H.A.M. Spinal cord compression during chronic epidural morphine administration in a cancer patient. Anaesthesia 42: 1201-1203, 1987.

Kaanders, J.H.A.M., van Daal, W.A.J., van der Kogel, A.J. and Hoogenraad, W.J. Radiotherapie bij hoofd-, halstumoren, fractionering (dutch). Gamma 38: 304-307, 1988.

Barentsz, J.O., Lemmens, J.A.M., Ruijs, J.H.J., Boskamp, E.B., Hendrikx, A.J.M., Karthaus, H.F.M., Kaanders, J.H.A.M. and Rosenbusch, G. Carcinoma of the urinary bladder: MR imaging with a double surface coil. Am. J. Radiol. 151: 107-112, 1988.

Ang, K.K., Jiang, G.-L., Frankenthaler, R.A., Kaanders, J.H.A.M., Garden, A.S., Delclos, L. and Peters, L.J. Carcinomas of the nasal cavity. Radiother. Oncol. 24: 163-168, 1992.

Kaanders, J.H.A.M., Fleming, T.J., Ang, K.K., Maor, M.H. and Peters, L.J. Devices valuable in head and neck radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 23: 163-168, 1992.

Kaanders, J.H.A.M., van Daal, W.A.J., Hoogenraad, W.J. and van der Kogel, A.J. Accelerated fractionation for laryngeal cancer, acute and late toxicity. Int. J. Radiat. Oncol. Biol. Phys. 24: 497-503, 1992.

Pop, L.A.M., Kaanders, J.H.A.M. and Heinerman, E.C.M. High dose rate intracavitary brachytherapy of early and superficial carcinoma of the nasal vestibule as an alternative to low dose rate interstitial radiation therapy. Radiother. Oncol. 27: 69-72, 1993.

Kaanders, J.H.A.M. and van der Maazen, R.W.M. A convenient and reliable method for carbogen breathing in man. Radiother. Oncol. 29: 341-343, 1993.

Kaanders, J.H.A.M. and Ang, K.K. Early reactions as dose-limiting factors in radiotherapy. Sem. Radiat. Oncol. 4: 55-67, 1994.

Mulder, S.J. and Kaanders, J.H.A.M. Een gemakkelijke en betrouwbare methode van carbogeengas ademen tijdens radiotherapie (dutch). Gamma 44: 221-223, 1994.

Kaanders, J.H.A.M., Pop, L.A.M., Muytjens, H.L., Bruaset, I. and van Daal, W.A.J. Topical administration of antimicrobial agents to prevent irradiation mucositis of the oral cavity and oropharynx: a pilot study. Radiat. Oncol. Invest. 2: 283-290, 1995.

Van der Maazen, R.W.M., Thijssen, H.O.M., Kaanders, J.H.A.M., de Koster, A., Keyser, A., Prick, M.J.J., Grotenhuis, J.A., Wesseling, P. and van der Kogel, A.J. Conventional radiotherapy combined with carbogen breathing and nicotinamide for malignant gliomas. Radiother. Oncol. 35: 118-122, 1995.

Kaanders, J.H.A.M., Pop, L.A.M., Marres, H.A.M., van der Maazen, R.W.M., van der Kogel, A.J. and van Daal, W.A.J. Radiotherapy with carbogen breathing and nicotinamide in head and neck cancer: feasibility and toxicity. Radiother. Oncol. 37: 190-198, 1995.

Kaanders, J.H.A.M. Radiotherapie: principes en toepassingen. Met bijzondere aandacht voor het hoofd-halsgebied (dutch). Ned. Tijdschr. Tandheelk. 103: 350-353, 1996.

Kaanders, J.H.A.M., Stratford, M.R.L., Liefers, J., Dennis, M.F., van der Kogel, A.J., van Daal, W.A.J. and Rojas, A. Administration of nicotinamide during a five- to seven-week course of radiotherapy: pharmacokinetics, tolerance, and compliance. Radiother. Oncol. 43: 67-73, 1997.

Bussink, J., Kaanders, J.H.A.M., Rijken, P.F.J.W., Martindale, C.A. and van der Kogel, A.J. Multi-parameter analysis of vasculature, perfusion and proliferation in human tumour xenografts. Br. J. Cancer 77: 57-64, 1998.

Kaanders, J.H.A.M., Pop, L.A.M., Marres, H.A.M., Liefers, J., van den Hoogen, F.J.A., van Daal, W.A.J. and van der Kogel, A.J. Accelerated radiotherapy with carbogen and nicotinamide (ARCON) for laryngeal cancer. Radiother. Oncol. 48: 115-122, 1998.

Bussink, J., Kaanders, J.H.A.M., Rijken, P.F.J.W., Peters, J.P.W., Hodgkiss, R.J., Marres, H.A.M. and van der Kogel, A.J. Vascular architecture and microenvironmental parameters in human squamous cell carcinoma xenografts: effects of carbogen and nicotinamide. Radiother. Oncol., accepted.

Kaanders, J.H.A.M., van der Kogel, A.J. and Ang, K.K. Altered fractionation: limited by mucosal reactions? Radiother. Oncol., accepted.

Book and chapters

Ang, K.K., Kaanders, J.H.A.M. and Peters, L. J. Radiotherapy for Head and Neck Cancers: Indications and Techniques. Lea & Febiger, Philadelphia, PA, 1994.

Lenarz, T., Schmoll, H.-J., Kaanders, J.H.A.M., Marres, H.A.M., Bruaset, I., Pop, L.A.M. and de Mulder, P.H.M. Speicheldrüsenmalignome (german). In: Kompendium Internistische Onkologie. 2nd edition, Vol. 2, pp 410-420. Editors: Schmoll, H.-J., Höffken, K. and Possinger, K. Springer-Verlag, Berlin, 1997.

Kaanders, J.H.A.M., Issing, P.R., Pop, L.A.M., Lenarz, T., de Mulder, P.H.M., Schmoll, H.-J. and Marres, H.A.M. Hypopharynxkarzinom (german). In: Kompendium Internistische Onkologie. 2nd edition, Vol. 2, pp 450-460. Editors: Schmoll, H.-J., Höffken, K. and Possinger, K. Springer-Verlag, Berlin, 1997.

Kaanders, J.H.A.M., Lenarz, T., Pop, L.A.M., Schmoll, H.-J., de Mulder, P.H.M. and Marres, H.A.M. Larynxkarzinom (german). In: Kompendium Internistische Onkologie. 2nd edition, Vol. 2, pp 461-480. Editors: Schmoll, H.-J., Höffken, K. and Possinger, K. Springer-Verlag, Berlin, 1997.

Stellingen

behorende bij het proefschrift

Accelerated radiotherapy with

carbogen and nicotinamide

for carcinomas of the head and neck

A study on feasibility, toxicity and tumor response

J.H.A.M. Kaanders

Nijmegen, 9 december 1998

1. Rational and stepwise incorporation of well-established radiobiological principles in clinical trials definitely leads to important improvements in treatment outcome. The question is not *if*, but *how* to implement these principles in the daily practice of radiotherapy.
   This thesis.

2. The additional costs of ARCON-treatment relative to conventional radiotherapy amount to 100 Dutch guilders per patient. When ARCON is compared with other experimental treatments including chemotherapy, immunotherapy and conformal radiotherapy, there seems to be an inverse relationship between the costs of these treatments and the therapeutic gain.

3. For radiotherapy of head and neck tumors, relative to a conventional treatment of 7 weeks, the maximum achievable gain in treatment time is 2 weeks with the mucosa being the limiting tissue. Any further acceleration requires a reduction of dose.
   This thesis.

4. Every patient presenting with a larynx carcinoma should be considered for an organ preserving treatment.
   This thesis.

5. Of all new treatment strategies for head and neck cancer, accelerated radiotherapy is currently the most successful in randomized clinical trials. A strong case can be made for the introduction of this approach as the standard treatment for certain patient categories.

6. Limited machine capacity is an invalid argument for not using accelerated radiotherapy.
   This thesis.

7. The distinction between acute and chronic hypoxia is a major simplification of a condition with continual temporal and spatial fluctuations of both oxygen delivery and oxygen consumption.

8. "Radiotherapeutische behandeling" is een pleonasme. Het is beter om "radiotherapie" of "bestralingstherapie" te zeggen.

9. Kwaliteitsbevordering is in de mode, ook binnen de gezondheidszorg. In hoeverre dit zal leiden tot een daadwerkelijk betere behandeling van de patiënt valt nog te bezien.

10. De aanduiding "millenniumprobleem" is niet correct. Het probleem wordt immers veroorzaakt door een eeuwwisseling en dient daarom "centenniumprobleem" te heten. Het feit dat deze eeuwwisseling samenvalt met een millenniumwisseling is geen reden om het probleem buiten proporties op te blazen.

11. Als het centenniumprobleem is opgelost zijn we de komende acht millennia uit de zorgen.

ISBN 90-9012228-1